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UNIVERSITY OF ALBERTA

SYNTHESIS OF CARBAZOMYCIN B
AND
DEVELOPMENT OF A RADICAL ROUTE TO AMINO ACIDS

BY

NOLA ETKIN ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta
SPRING 1994

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled SYNTHESIS OF CARBAZOMYCIN B AND DEVELOPMENT OF A RADICAL ROUTE TO AMINO ACIDS submitted by NOLA ETKIN in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

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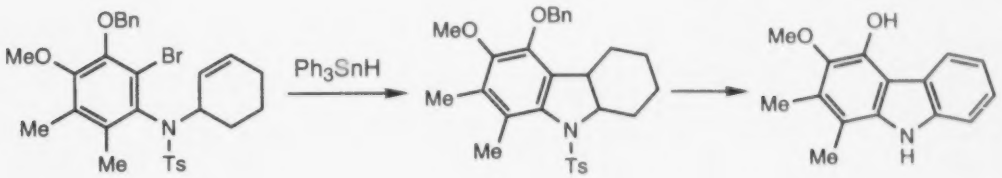
To Brenda

ABSTRACT

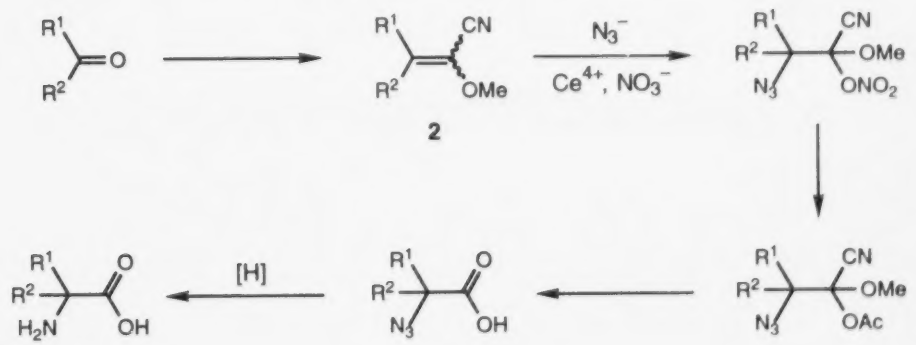
The first part of this thesis describes the synthesis of the carbazole-containing antibiotic Carbazomycin B (**1**) by radical cyclization methodology (Scheme A).



1

Scheme A

The second part describes the development of a method for the synthesis of amino acids based on the addition of azido radicals to methoxyacrylonitriles **2** (Scheme B). A two-stage hydrolysis of the initial adducts gives azido acids **3**, which are transformed by standard methods into the amino acids **4**.



2 **3** **4**

Scheme B

ACKNOWLEDGEMENTS

I want to express my sincere gratitude and appreciation to the many people who have supported and encouraged me over the past years. Particular thanks is due

to my supervisor, Dr. D. L. J. Clive;

to my good friend and colleague, Michel Cantin, for his continuous support, and for making the whole experience more rewarding and enjoyable;

to my friend, Aruna Sharma, for the benefit of her experience;

to my co-workers, especially Chengzhi Zhang, Maarten Postema, Don Middleton, Luc Bordeleau, Peter Vernon, and Taryn Boivin, for helping to provide a more pleasant environment, and for invaluable assistance;

to Dr. Margaret-Ann Armour, for many long discussions, and for her sage advice;

to Dr. Byron Kratochvil, Dr. Jeff Stryker, Dr. Bill Ayer, Dr. Karl Kopecky, and Dr. Ted McClung, for their support and encouragement;

to the technical and support staff of the Department of Chemistry for their excellent service and dedication; particular thanks to the NMR and mass spectral technical staff, to Dr. B. D. Santarsiero and Dr. R. McDonald for determination of an X-ray structure, and to Dr. J. W. Lown and Dr. T. Joseph for molecular modelling;

to the Natural Sciences and Engineering Research Council of Canada and the Department of Chemistry for financial support;

to my family, for their never-wavering faith in me, and for constant love and support;

and, most importantly, to my life partner, Brenda Smith, for standing beside me throughout everything, and for making it all worthwhile.

TABLE OF CONTENTS

	Page
Part I Synthesis of Carbazomycin B	1
I Introduction	2
Origin and Structure of the Carbazomycins	2
Biological Activity	5
Synthetic Approaches to Carbazoles	5
Synthesis of the Carbazomycins and Related Alkaloids	17
Proposed Synthesis of Carbazomycin B	26
II Discussion	29
Model Studies	29
Preparation of Cyclization Precursors	30
Radical Cyclizations	37
Completion of the Synthesis	41
Mechanistic Studies	42
Origin of the Isomerism	49
Conclusion	59
III Experimental	61
IV References & Footnotes	120

TABLE OF CONTENTS (continued)

	Page
Part II Development of a Radical Route to Amino Acids	126
I Introduction	127
Methods of Amino Acid Synthesis	127
Radical Techniques in Amino Acid Synthesis	133
Previous Studies of Radical Addition in Amino Acid Synthesis	137
II Discussion	140
Addition of Carbon Radicals to *N*-Stannyl Ketenimines	140
Addition of Carbon Radicals to Other Acceptors	142
Intermolecular Addition of Nitrogen Radicals	144
Azidonitrations	151
Stereoselectivity of the Reaction	166
Mechanistic Considerations	172
Conclusion	179
III Experimental	181
IV References & Footnotes	212

LIST OF TABLES

Page

Part I Synthesis of Carbazomycin B

Table 1 Radical Cyclizations 38

Table 2 $t_{1/2}$ for Racemization of Sulfonamides **149** 58

Part II Development of a Radical Route to Amino Acids

Table 3 Synthesis of Methoxyacrylonitriles 157

Table 4 Synthesis of Azido Acids and Amino Acids 159

LIST OF FIGURES

Page

Part I Synthesis of Carbazomycin B

Figure 1 Isomer Ratio versus Temperature for Compounds **95** & **114** 50

Figure 2 X-ray Crystal Structure for Compound **140a** 52

Figure 3 Calculated Minimum Energy Conformation for Major Isomer of Compound **140** 54

Figure 4 Calculated Minimum Energy Conformation for Second Isomer of Compound **140** 55

Figure 5 Calculated Conformation for Compound **140** (Major Isomer) 117

Figure 6 Calculated Conformation for Compound **140** (Second Isomer) 118

LIST OF ABBREVIATIONS

AIBN	azobisisobutyronitrile
Boc	*tert*-butoxycarbonyl
c-C_6H_{11}	cyclohexyl
CAN	ceric ammonium nitrate
CIMS	chemical ionization mass spectrum
CPK	Corey-Pauling-Kulton
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
i-Pr, *i*-Prop	isopropyl
m-CPBA	*m*-chloroperoxybenzoic acid
PCC	pyridinium chlorochromate
Phth	phthaloyl
PPA	polyphosphoric acid
pyr	pyridine (or 2-pyridyl)
SCE	saturated calomel electrode
TBAF	tetrabutylammonium fluoride
Tf	trifluoromethanesulfonyl
THF	tetrahydofuran
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
TSP	sodium 3-trimethylsilylpropionate-2,2,3,3-d_4

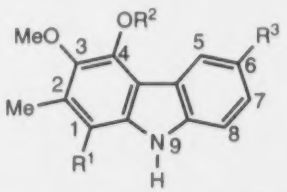
Part I

Synthesis of Carbazomycin B

I INTRODUCTION

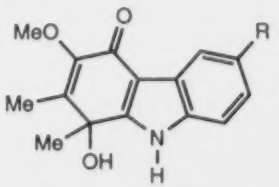
Origin and Structure of the Carbazomycins

Carbazomycins A (**1**) and B (**2**) were first isolated from an unidentified *Streptomyces* in 1980 by Nakamura and co-workers[1]. Later, carbazomycins C–F (**3**–**6**)[2,3] and the quinol-containing carbazomycins G (**7**) and H (**8**)[4] were isolated from the same microorganism, assigned as a strain of *Streptoverticillium ehimense*.[5]



Carbazomycin A (**1**): R^1 = Me, R^2 = Me, R^3 = H
Carbazomycin B (**2**): R^1 = Me, R^2 = H, R^3 = H
Carbazomycin C (**3**): R^1 = Me, R^2 = H, R^3 = OMe
Carbazomycin D (**4**): R^1 = Me, R^2 = Me, R^3 = OMe
Carbazomycin E (**5**): R^1 = CHO, R^2 = H, R^3 = H
Carbazomycin F (**6**): R^1 = CHO, R^2 = H, R^3 = OMe

Both the unique structure and the unusual biological activity of the carbazomycins have gained them considerable attention.

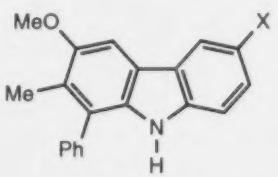


Carbazomycin G (**7**): R = H
Carbazomycin H (**8**): R = OMe

The carbazomycins differ in structure from other natural carbazoles as they have a C-14 skeleton, and a 1,2,3,4-tetrasubstituted nucleus.[5]

The structures of carbazomycins B, C, and G were confirmed by X-ray analysis,[1c,4] and carbazomycin G was shown to exist as a racemate.[4]

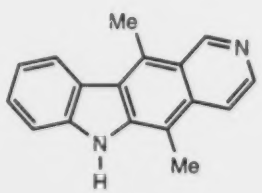
The structurally related marine alkaloids hyellazole (**9**) and 6-chlorohyellazole (**10**) were isolated from the blue-green alga *Hyella caespitosa* in 1979.[6] These, too, have an unusual substitution pattern on the carbazole nucleus.



Hyellazole (**9**): X = H

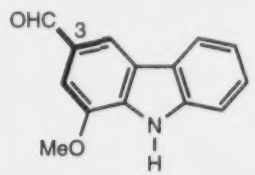
6-Chlorohyellazole (**10**): X = Cl

Prior to the isolation of the carbazomycins and the hyellazoles, the only known natural carbazoles were the pyridocarbazoles, of which the powerful antitumor agent ellipticine[7] (**11**) is the most noteworthy example, and the carbazoles isolated from *Rutaceae*.[8]



11

The carbazoles from *Rutaceae*, which appears to be the only family of higher plants to synthesize the carbazole nucleus, belong to three distinct groups, having a C–13, C–18, or C–23 skeleton. The first of these to be isolated was Murrayanine (**12**) which, like all members of this compound class, bears a one-carbon substituent in the C–3 position, a feature lacking in the carbazomycins. Other members have methyl or carboxyl groups in this position.



12

It has been suggested that 3-methylcarbazole is a common intermediate in the formation of the carbazole alkaloids of *Rutaceae*, and that the five carbons marked in bold in **12** are derived from mevalonate.[9] The incorporation of mevalonic acid has been shown, but its location has not been determined. It has been found, however, that the extra C-3 carbon is not derived from a one-carbon unit (i.e. from methionine).[10]

In contrast, the carbazole nucleus of carbazomycin B is found to derive from tryptophan and pyruvate.[5,11] This is the only natural carbazole for which the biosynthetic pathway has been completely elaborated.

Biological Activity

The carbazomycins were noticed because of their unusual biological activity, being the first carbazoles to exhibit antibiotic properties. The major component, carbazomycin B, is also the most highly active.[1a]

Carbazomycin B inhibits the growth of some phytopathogenic fungi, and has weak antibacterial and anti-yeast activities.[1a] Carbazomycin C also shows weak inhibition of some bacteria and fungi,[3] while carbazomycins A, D, G and H have only extremely weak antibiotic properties.[1a,3,4]

Other workers have found that carbazomycins E and F inhibit formation of aerial mycelia, but found no antibiotic activity against fungi and bacteria for these compounds.[2]

It appears from these observations that the free phenolic hydroxyl group is essential to the biological activity of the carbazomycins.

Recently, it was found that a carbazomycin-containing fermentation extract showed significant inhibition of 5-lipoxygenase, one of the enzymes responsible for the control of allergic response. This inhibitory activity peaks with carbazomycin B, although carbazomycin C is also active. It is speculated that this inhibition is due to radical scavenging activity, for which the free phenolic hydroxyl group may again be necessary.[12]

Synthetic Approaches to Carbazoles

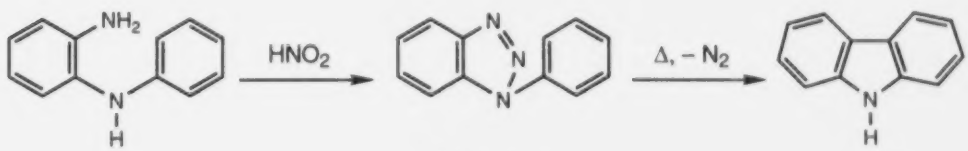
Several of the synthetic approaches used for the synthesis of

carbazoles are simply extensions of classical methods for formation of indoles, although some routes specific to the formation of carbazoles have also been developed.[13]

a) Early Methods

In the major early methods for the synthesis of carbazoles it is the central C-C bond which is formed in the critical step.[14]

In the Graebe-Ullmann method[15] (Scheme 1), an *o*-amino aniline is treated with nitrous acid to give the intermediate triazole which, upon losing nitrogen, gives the carbazole product.

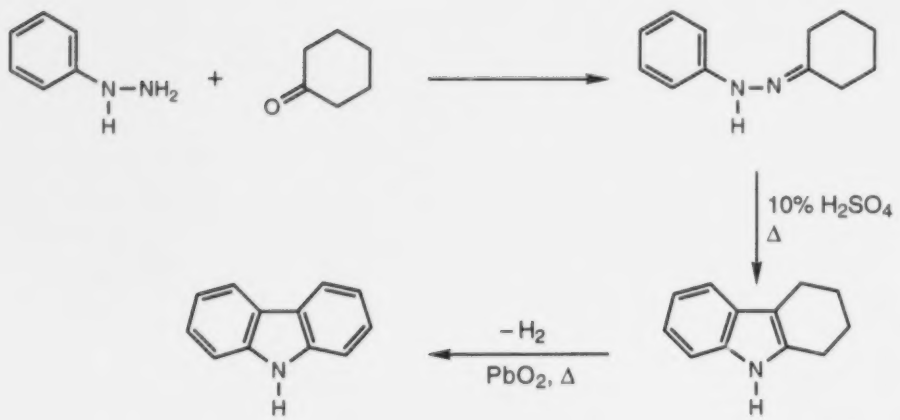


Scheme 1

This method has been used fairly extensively, although it generally requires vigorous heating (usually upwards of 350°C) for decomposition of the triazole intermediate.

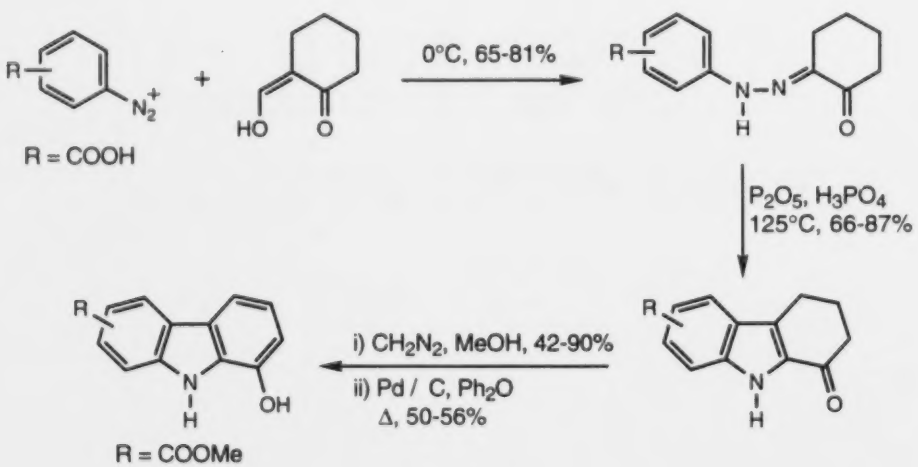
Borsche's method[16] (Scheme 2), which is an application of the Fischer indole synthesis, involves condensation of an aryl hydrazine with cyclohexanone to give the corresponding hydrazone which, on heating in acid, gives the usual Fischer product. Dehydrogenation of the tetrahydrocarbazole by classical methods completes Borsche's sequence.

A recent approach to 1-hydroxycarbazoles (Scheme 3)[17] followed a similar route. The hydrazone was formed by the Japp-



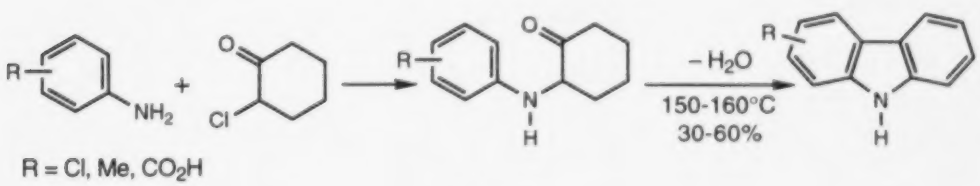
Scheme 2

Klingemann reaction, in which a diazonium salt (formed from the corresponding amine) is mixed with 2-hydroxymethylene cyclohexanone to provide the indicated α-ketohydrazone. This method gives a cleaner product, and better overall yields than the classical sequence. Treatment with acid gives good yields of the dihydrocarbazole. Esterification of the acid substituents prior to dehydrogenation results in moderate yields of the 1-hydroxycarbazoles.



Scheme 3

Carbazoles have also been formed by an extension of the Bischler synthesis. According to this protocol, α-anilino-cyclohexanones, which result from the alkylation of anilines with α-chloro-cyclohexanone, are cyclized by electrophilic attack on the carbonyl. Dehydration and oxidation give the carbazole derivatives (Scheme 4).[18]

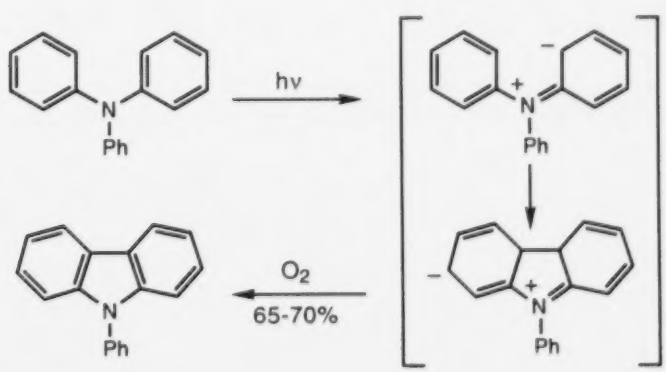


Scheme 4

b) Coupling of Diphenylamines

Another method which has been used extensively is the oxidative coupling of diphenylamines. Here too, it is the central C-C bond which is formed.

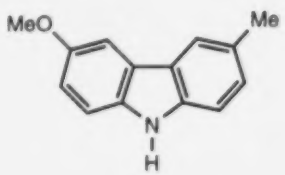
This reaction was first observed as the ultraviolet-initiated decomposition of diphenylamine to give carbazole.[19] Considerable



Scheme 5

effort has been put into mechanistic studies, and the following mechanism has been proposed[20] (Scheme 5). Excitation of the aryl-aniline gives the zwitterionic intermediate, which cyclizes to the observable (in the absence of oxygen) tricyclic intermediate, which is then oxidized to the carbazole.

Carruthers[21] has applied this strategy to the synthesis of the alkaloid glycozoline (**13**).



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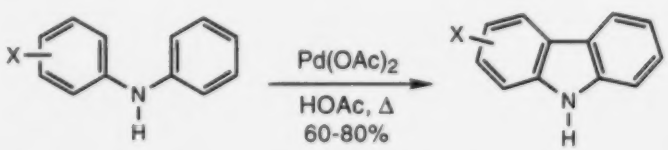
The coupling of diphenylamines can also be accomplished by the action of palladium acetate (Scheme 6).[22] This reaction is suited to a variety of substituents, and is now considered to be the best method for the coupling of diphenylamines.

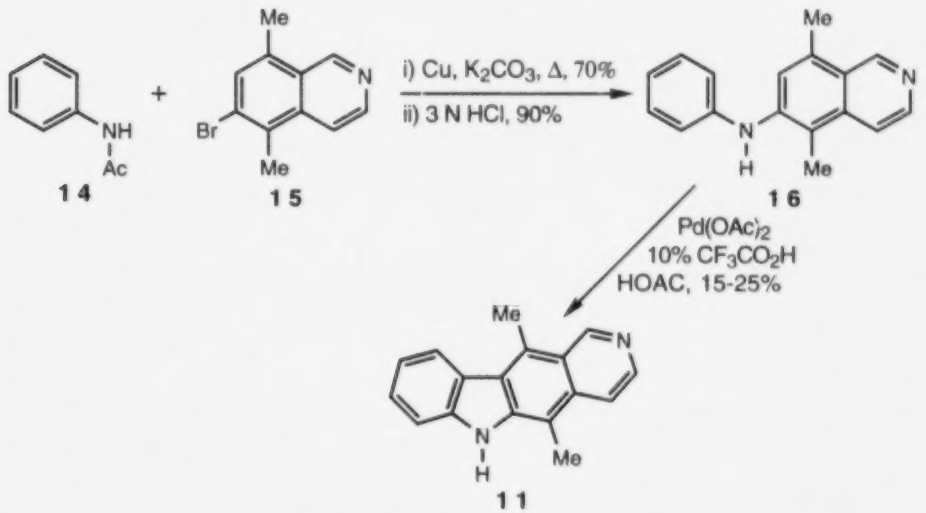


X = Me, MeO, Cl,
Br, NO_2, CO_2H

Scheme 6

This palladium-induced coupling was used in a short synthesis of ellipticine (**11**).[23] The two fragments **14** and **15** (Scheme 7) were joined using the Goldberg modification of the Ullmann

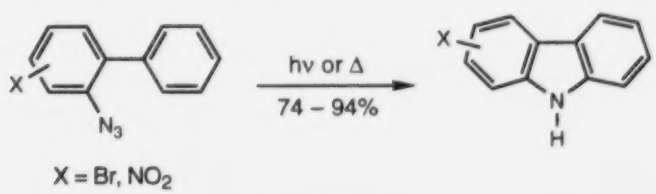
coupling. Hydrolysis of the amide gave the arylaniline **16**. Although a model lacking the pyridine ring could be cyclized photolytically, ellipticine itself is very light sensitive, and so could not be detected under those conditions. Treatment with palladium acetate, however, gave a modest yield of ellipticine.



Scheme 7

c) Nitrene Insertion

In another often-used approach it is the N-C bond which is formed. Nitrenes, generated by thermal or photochemical decomposition of biphenyl azides, insert into aromatic C-H bonds to give

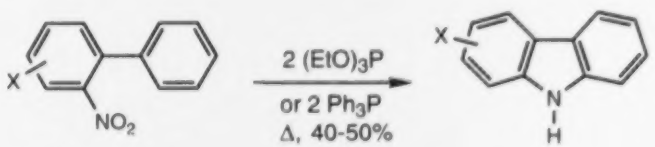


X = Br, NO_2

Scheme 8

generally good yields of the carbazole products (Scheme 8).[24]

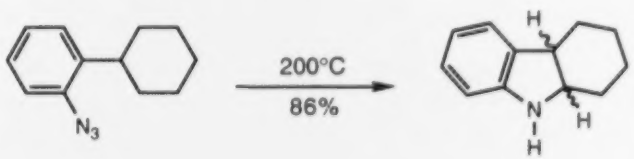
Alternatively, in the Cadogan reaction, the nitrenes are generated from nitro compounds, by deoxygenation with tertiary phosphines or phosphites[25] (Scheme 9). The reaction is usually carried out in refluxing triethyl phosphite. Tristrimethylsilylphosphite has been recommended as an alternate reagent, as it requires lower temperatures and shorter reaction times, and the by-products are easily removed after hydrolysis.[26]



X = Cl, Br, Me

Scheme 9

Nitrenes can also insert into aliphatic C-H bonds, thereby yielding hexahydrocarbazoles[27] (Scheme 10).

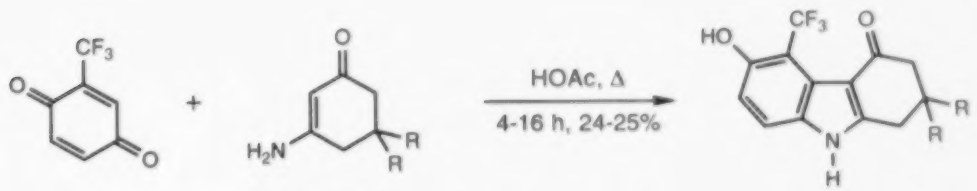


Scheme 10

d) Nenitzescu Synthesis

An extension of the Nenitzescu indole synthesis has also been applied to the synthesis of carbazole derivatives. In this method, either the central C-C bond, or the N-C bond may be formed last.

In one example, treatment of enamines **17** with 2-trifluoromethyl-1,4-benzoquinone gave the hydrocarbazoles **18** in modest yields (Scheme 11).[28] In this case, the enamine is thought to add in a conjugate fashion to the quinone, followed by condensation of the amine.



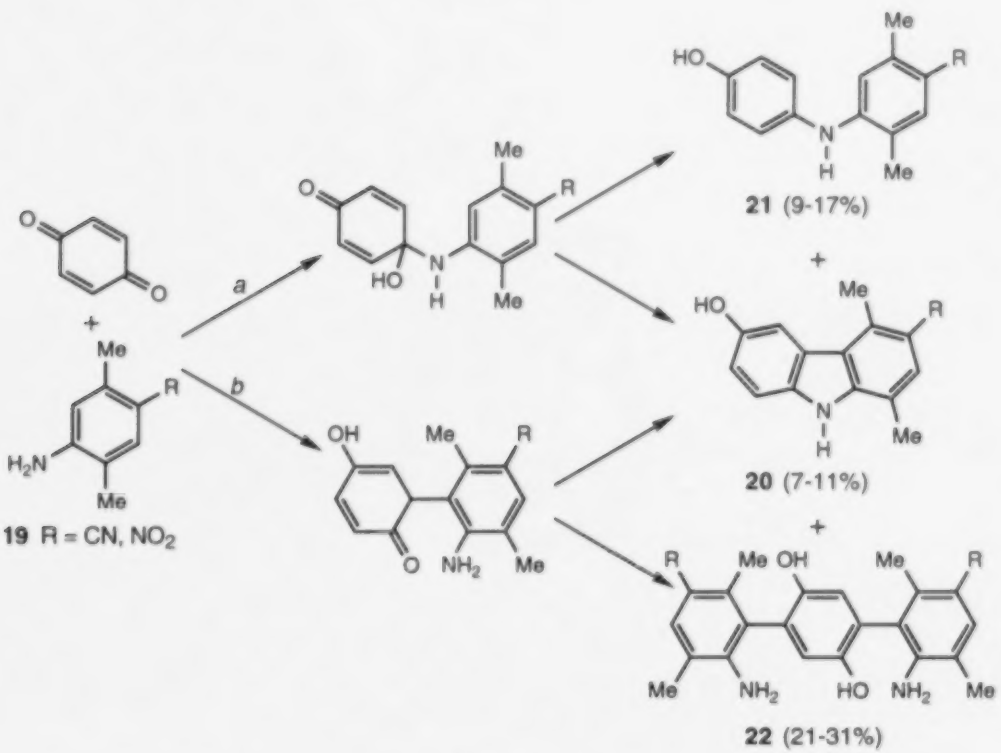
17 R = H, Me **18**

Scheme 11

Another application of the Nenitzescu synthesis uses *p*-cyano- or *p*-nitroanilines **19** (Scheme 12) as the enamine fragment.[29] Reaction with 1,4-benzoquinone in refluxing trifluoroacetic acid gives low yields of the carbazoles **20**, which are intermediates in the synthesis of ellipticine analogues.

The isolation of the main side-products **21** and **22** is an indication that several mechanisms may be in effect. Initial N-C condensation (route *a*, Scheme 12) would give the α-hydroxyaniline intermediate. Subsequent C-C attack gives the desired carbazole product **20**, or the intermediate could simply be reduced to **21**. Alternatively, initial C-C attack (route *b*, Scheme 12) to give the biphenyl intermediate, followed by N-C condensation could also account for the formation of the carbazole product. Attack of a second molecule of **19** on the biphenyl intermediate, followed by

oxidation would give the hydroquinone **22**. This initial C-C attack once again seems to be the major mode of reaction.



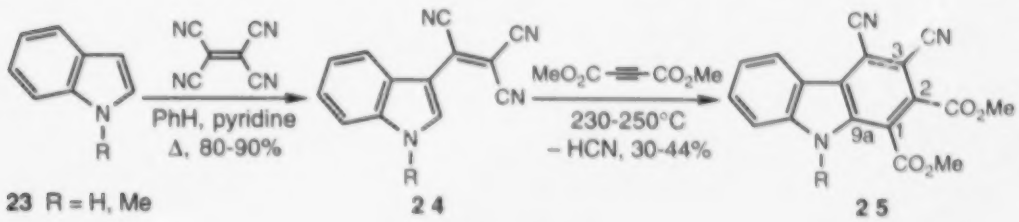
Scheme 12

e) Cycloaddition

Much recent work has focused on the use of cycloaddition reactions for the formation of the carbazole nucleus. Generally, the diene unit incorporates the indole nucleus, and the third ring is generated via a [4+2] cycloaddition.

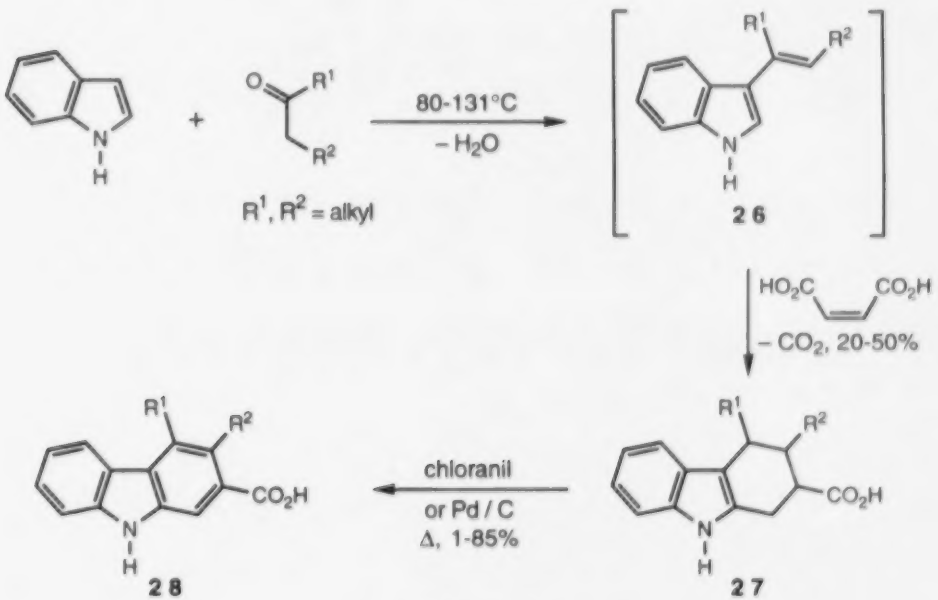
In one example, the 9a,1 and 2,3 bonds of the carbazole framework are formed by cycloaddition of dimethyl acetylenedicarboxylate with diene **24**, which is prepared by condensation of

indole **23** with tetracyanoethylene (Scheme 13).[30]



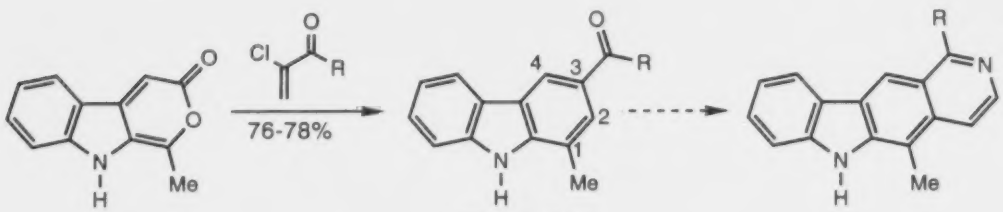
Scheme 13

In another example, condensation of indole with various ketones gives the dienes **26** (Scheme 14).[31] Diels-Alder reaction with maleic acid, and loss of carbon dioxide, then gives the tetrahydrocarbazoles **27**. Dehydration, either by using chloranil or by heating with palladium, gives generally low yields of the carbazole products **28**.



Scheme 14

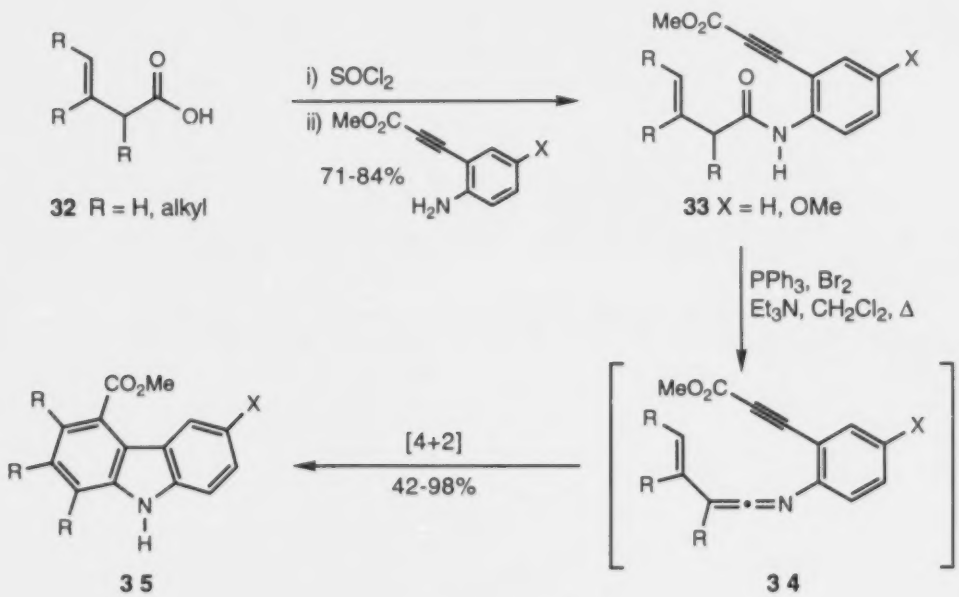
In another route, it is the 1,2 and 3,4 bonds which are formed in the cycloaddition. The indole α-pyrone **29** acts as dienophile when treated with vinyl chlorides to give, after loss of carbon dioxide and HCl, 1,3-substituted carbazoles **30** (Scheme 15).[32] Carbazole **30** (R = Me) was converted into the ellipticine analogue, olivacine (**31**, R = Me).



29 **30** R = H, Me **31**

Scheme 15

In an unusual variation, the indole nucleus is not preformed,



32 R = H, alkyl **33** X = H, OMe **34** **35**

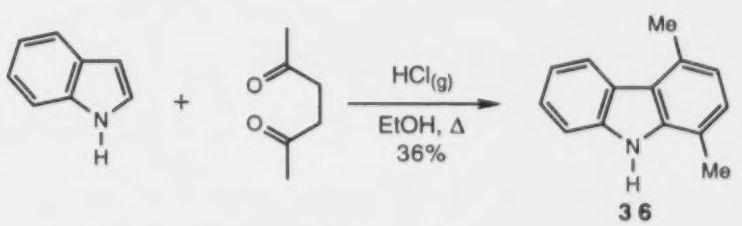
Scheme 16

but is assembled in a [4+2] cycloaddition that generates two rings of the carbazole framework at once (Scheme 16).[33] Amides **33** were prepared by condensation of the corresponding anilines with the acid chlorides generated from 3,4-unsaturated carboxylic acids **32**. The vinyl ketenimines **34** are generated from the amides by treatment with triphenylphosphine and bromine. Intramolecular Diels-Alder cycloaddition then gives, in one step, good yields of the carbazoles **35**.

f) From Other Indoles

Other methods have been developed to convert indoles into carbazoles.

An early synthesis of ellipticine relied on the annulation of indole by acid-catalyzed condensation with 2,5-hexanedione to form the carbazole nucleus.[34] The resulting carbazole **36** (Scheme 17) was converted into ellipticine in four steps.

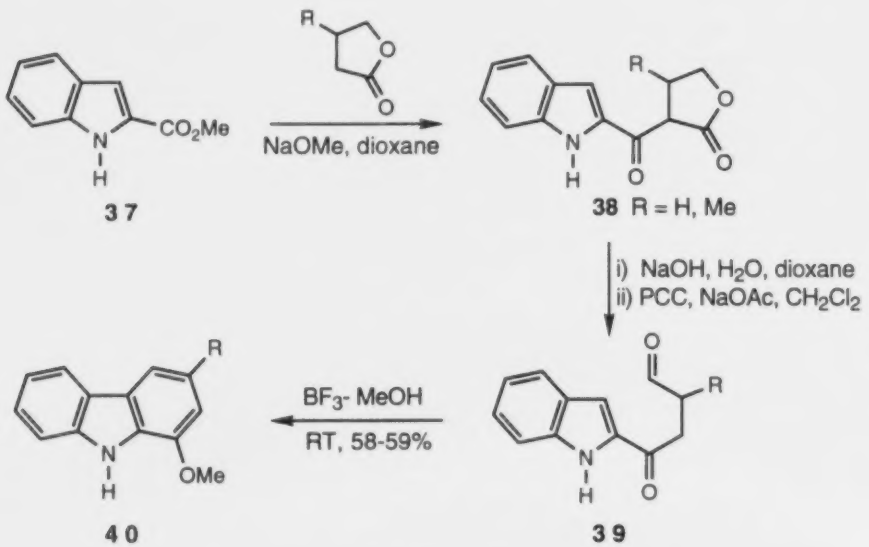


36

Scheme 17

A recent approach to 1-alkoxycarbazoles involved the electrophilic ring closure of aldehydes **39** (Scheme 18).[35] The aldehydes were prepared from the indole esters **37** by condensation with butyrolactones by way of the β-keto lactones **38**. Lactone

hydrolysis, with concomitant decarboxylation, followed by oxidation of the resulting alcohols gave the required aldehydes. The ring closure was effected by treatment with boron trifluoride-methanol to give the carbazole alkaloid Murrayafoline A (**40**, R = Me).



Scheme 18

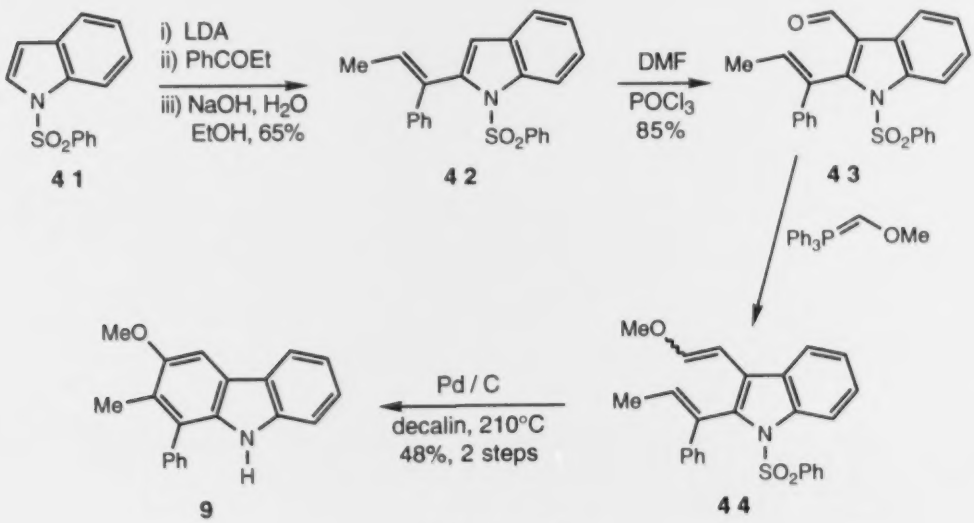
Synthesis of the Carbazomycins and Related Alkaloids

Several groups have worked on the synthesis of carbazomycins A and B, as well as the hyellazoles.[36-44] These alkaloids share a common substitution pattern of the carbazole framework, i.e. carbon substituents in the 1 and 2 positions, and an oxygen substituent in the 3 position.

Most of the approaches to these alkaloids have used cycloaddition or electrocyclic reactions to form the carbazole nucleus.

The first total synthesis of hyellazole (**9**) relied on the electrocyclic ring closure of divinyl indole **44** (Scheme 19).[36] Compound

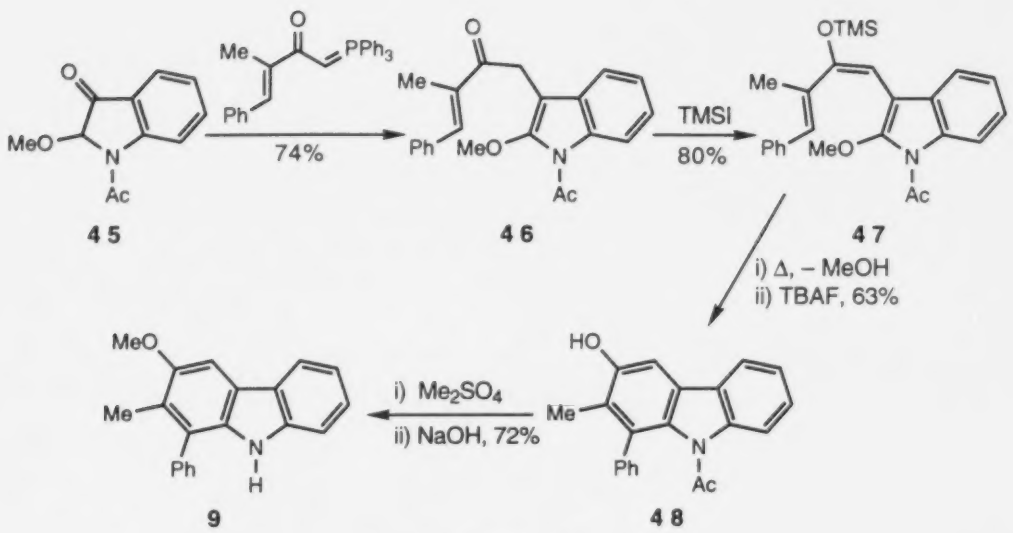
44 was prepared by addition of the anion of sulfonyl indole **41** to propiophenone, and dehydration of the resulting alcohol. The so-obtained vinyl indole **42** was converted to aldehyde **43** by treatment with the Vilsmeier reagent. Wittig reaction gave **44**, which was cyclized and dehydrogenated to hyellazole by heating over palladium. 6-Chlorohyellazole was prepared by a similar route.



41 **42** **43** **44** **9**

Scheme 19

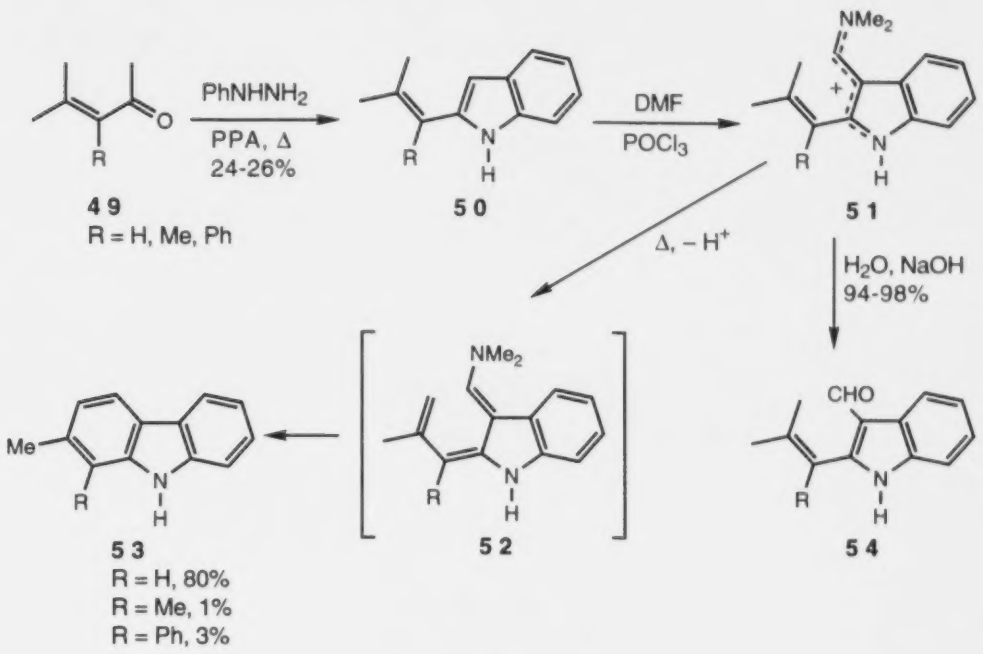
A more recent synthesis of hyellazole involved the electrocyclic ring closure of a different substrate (Scheme 20).[37] Wittig reaction of the 2-oxindole **45**, followed by silyl enol ether formation gave **47**. Ring closure, with concomitant loss of methanol, and then desilylation gave the carbazole product **48**, which was converted to hyellazole by methylation and hydrolysis of the amide.



Scheme 20

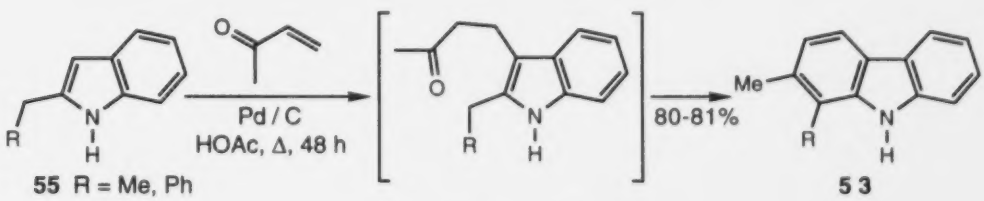
Other workers, in an attempt to develop a general route to 1,2-disubstituted carbazoles, examined the closure of indolenines **51**, formed by treatment of 2-vinylindoles **50** with the Vilsmeier reagent (Scheme 21).[38a,b] The vinylindoles were formed by Fischer indolization from the appropriate α,β-unsaturated ketones and phenylhydrazine in hot polyphosphoric acid. Although **53** was formed in good yield when there was no C(1) substituent (R = H), the yields in the substituted cases were very low. It was suggested that steric congestion makes it difficult for the intermediate **52** to form, or to reach the conformation required for closure in those cases.

The formation of consistently good yields of the usual hydrolysis products **54** after treatment with the Vilsmeier reagent is an indication that the formation of **51** is not the problem step in this sequence.



Scheme 21

The same authors describe a more general route to 1,2-disubstituted carbazoles using the alkylation of indoles **55** with α,β-unsaturated ketones (Scheme 22).[38a,c] The initial adducts are dehydrated and dehydrogenated by refluxing with palladium in acetic acid to give good yields of carbazoles **53**.



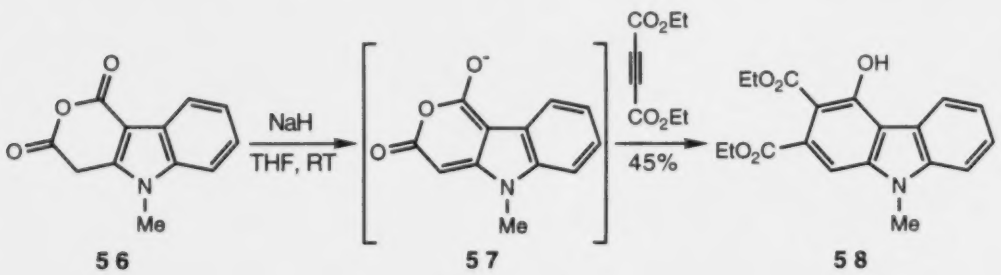
Scheme 22

In an attempt to extend this protocol to the synthesis of 4-methoxy carbazoles, the indole **55** (R = Me) was condensed with 4-

methoxy-3-buten-2-one. However, the methoxy group was lost in the course of the reaction, resulting once again in formation of carbazole **53**.

Other recent approaches have used the Diels-Alder reaction to assemble the carbazole.

The 4-hydroxycarbazole diester **58** (Scheme 23) was prepared from anhydride **56**. Deprotonation of **56** gave indole-2,3-orthoquino-dimethane analogue **57** which reacted with the dienophile to give, after loss of carbon dioxide, **58**.[39]



56 **57** **58**

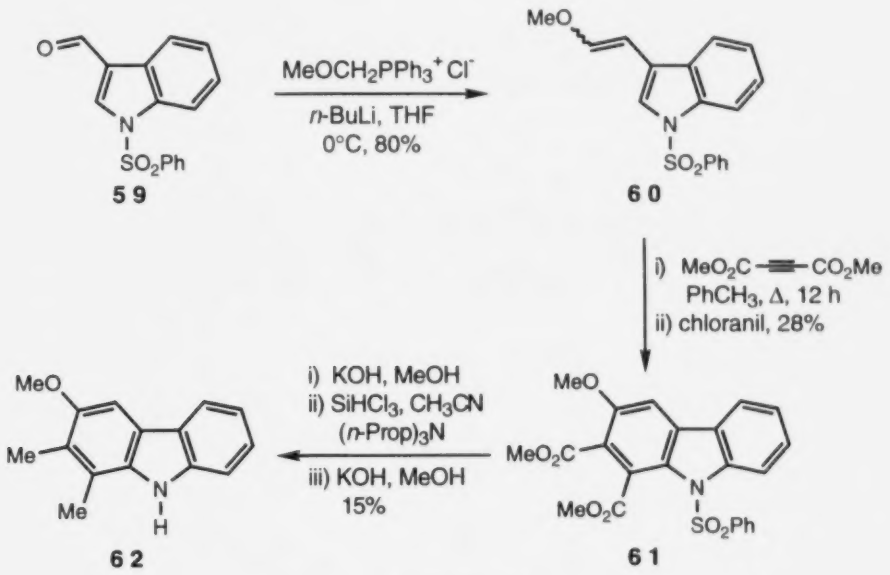
Scheme 23

More recent cycloaddition approaches have targeted carbazomycins A and B

The first such route to these compounds led to 4-demethoxycarbazomycin (**62**, Scheme 24).[40] The diene fragment **60** was assembled by Wittig reaction from indole-3-carboxaldehyde **59**. Cycloaddition with dimethyl acetylenedicarboxylate and dehydrogenation of the resulting adduct with chloranil gave a poor yield of carbazole **61**. The demethoxy derivative was a major side-product, resulting from elimination of methanol.

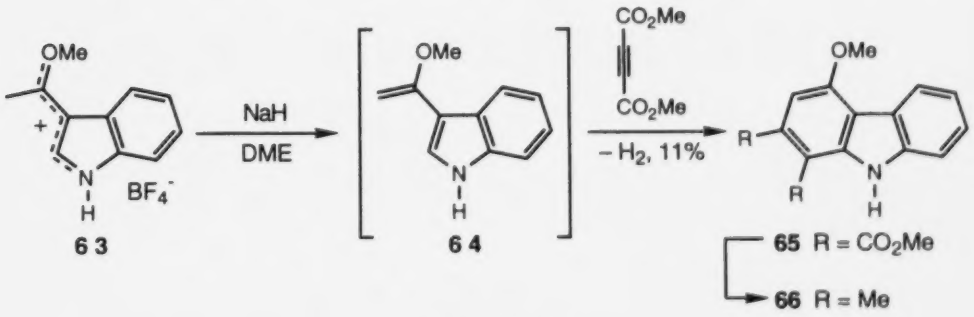
Hydrolysis of both the esters and the sulfonamide, and

reduction of the resulting dicarboxylic acid using trichlorosilane gave 4-demethoxycarbazomycin.



Scheme 24

A similar route was used to prepare 3-demethoxycarbazomycin (**66**, Scheme 25).[41] In this case, the diene **64** was generated by deprotonation of cation **63**. Diels-Alder reaction gave a low yield of the diester **65**, which was converted to 3-demethoxycar-

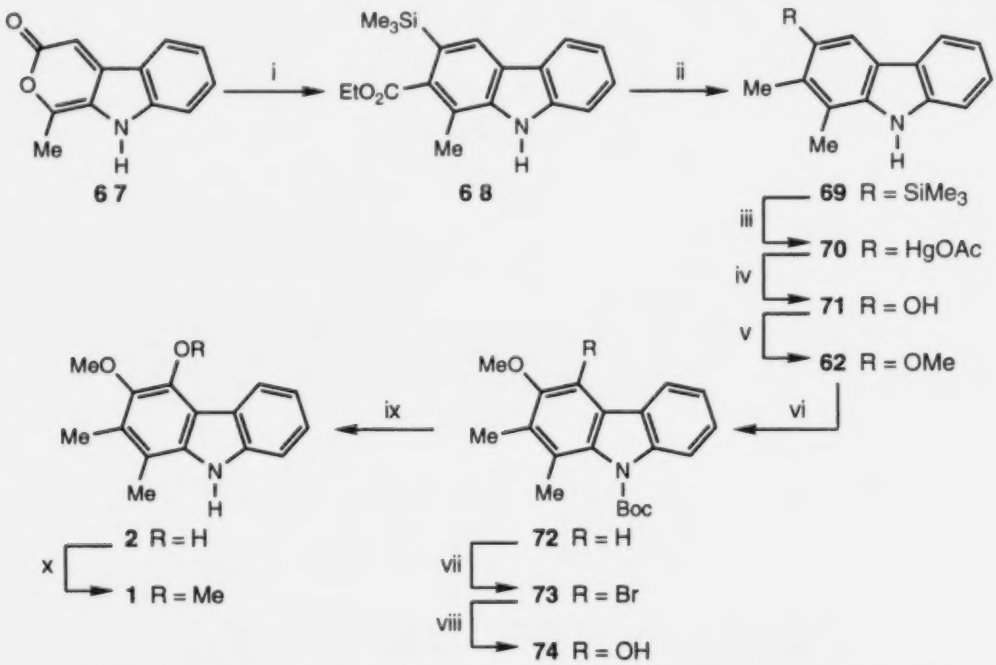


Scheme 25

bazomycin by the same sequence as described above in Scheme 24.

The first total synthesis of carbazomycins A and B based on Diels-Alder chemistry was reported in 1989 (Scheme 26).[42]

This route involved cycloaddition of indole α-pyrone **67** with ethyl 3-trimethylsilylpropynoate to assemble the carbazole framework. The alkyne component was chosen both to direct the regiochemistry, and because the trimethylsilyl group could later be transformed into the required hydroxyl group.



Reagents: i) $MeO_2CC{\equiv}CSiMe_3$, PhBr, reflux, 53-77%; ii) $LiAlH_4$, dioxane, reflux, 98%; iii) $Hg(OAc)_2$, HOAc, 66%; iv) BH_3-THF, then H_2O_2, OH^- workup, 85%; v) MeI, K_2CO_3, acetone, reflux, 95%; vi) $(Boc)_2O$, DMAP, CH_3CN, 95%; vii) NBS, CH_3CN, 95%; viii) t-BuLi, THF, -78°C, then $(MeO)_3B$, -78-0°C, then H_2O_2, NaOH, H_2O, 73%; ix) 180-190°C, 98%; x) MeI, K_2CO_3, acetone, reflux, 94%.

Scheme 26

The cycloaddition gave moderate to good yields of the trisub-

stituted carbazole **68**, with no evidence of the isomeric carbazole. This regioselectivity was ascribed to both steric and electronic effects.

Reduction of the ester gave directly the 2-methyl derivative **69**. Mercurio-desilylation, hydroboration, and oxidation served to introduce the 3-hydroxyl group, which was methylated to give 4-deoxycarbazomycin, **62**.

A limitation of this method is that it requires introduction of the 4-hydroxyl group at a late stage. All attempts at direct oxidation failed to introduce the required substituent.

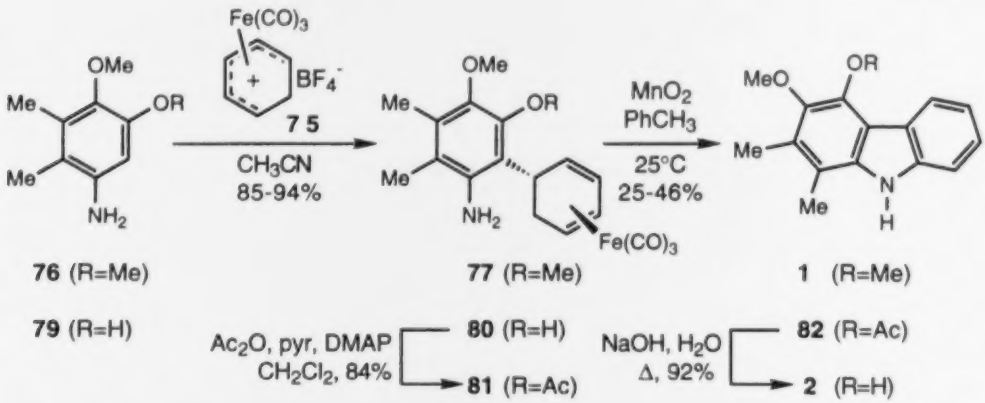
In a more circuitous route, the 4 position was first brominated, and then converted to the hydroxyl derivative. In order to brominate the desired position, it was necessary to first block the carbazole nitrogen, as direct bromination of **62** gave the 6-bromo derivative. The *N*-*t*-butoxycarbonyl carbazole **72** (see Scheme 26) could be brominated selectively to **73**. Lithium-halogen exchange, followed by reaction with trimethylborate gave, after oxidation, the required carbazole **74**. The protective group was removed on heating to give carbazomycin B (**2**), which was methylated to afford carbazomycin A (**1**).

An analogous route (cf. **67** → **62**) was used to prepare hyellazole (**9**) in 21% overall yield from the corresponding phenyl substituted indole α-pyrone.[42]

A new method of carbazole formation[43] has recently been applied to the synthesis of carbazomycins A and B.[44]

The iron complex **77** (Scheme 27), prepared from aniline **76**

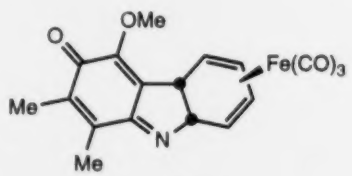
by electrophilic aromatic substitution with the iron-complexed cation **75**, is oxidatively cyclized with very active manganese dioxide to give, directly, carbazomycin A in 25% yield.



Scheme 27

A side product isolated (in 17% yield) from the oxidation is the iron-complexed iminoquinone **78** which results from oxidation of the initially formed dihydrocarbazole. Compound **78** can be converted into carbazomycin A by demetallation (trimethylamine *N*-oxide) and methylation of the resulting 3-hydroxycarbazole.

In fact, better overall yields of **1** are obtained by selective preparation of iminoquinone **78** (in 63% yield) using commercial manganese dioxide in place of the very active reagent normally employed for oxidation of **77**.



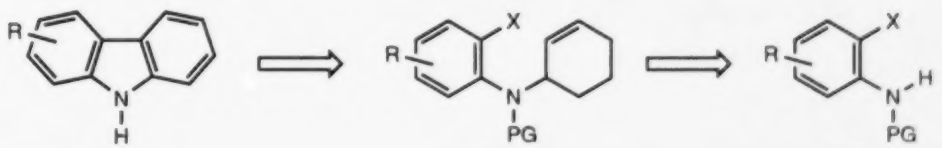
78

This methodology has also been applied to the synthesis of carbazomycin B. The iron-complex **80** (Scheme 27), prepared as above from aminophenol **79**, failed to cyclize when treated with manganese dioxide. The *O*-acetyl derivative **81**, however, gave 4-*O*-acetylcarbazomycin, **82**, in 46% yield, and ester hydrolysis then gave carbazomycin B.

Proposed Synthesis of Carbazomycin B

Although radical cyclization methodology has proved to be very useful in the formation of 5-membered carbocycles and heterocycles,[45] it has not yet been applied to the synthesis of carbazoles. We were interested in trying this methodology for the synthesis of carbazomycin B.

We envisaged the formation of carbazoles **83** (Scheme 28) from suitably constituted anilines **84**, containing a homolizable group (X = Br, I, etc.) *ortho* to the nitrogen. 5-*Exo* radical cyclization, and aromatization of the resulting system would provide the required carbazole framework. The requisite intermediate **84** should be accessible by alkylation of anilines **85**.

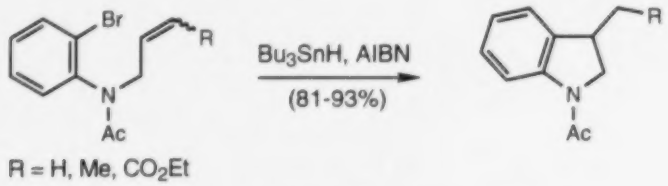


83 **84** **85**

Scheme 28

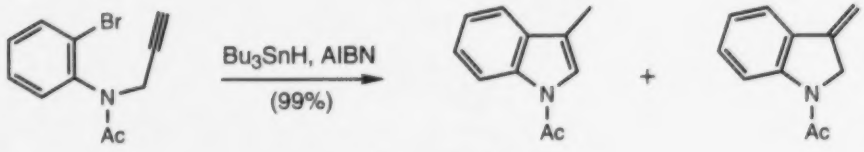
The cyclization of *o*-anilino radicals has been reported. For

example, a recent publication has detailed the formation of dihydroindoles from *N*-allyl anilines (Scheme 29).[46]



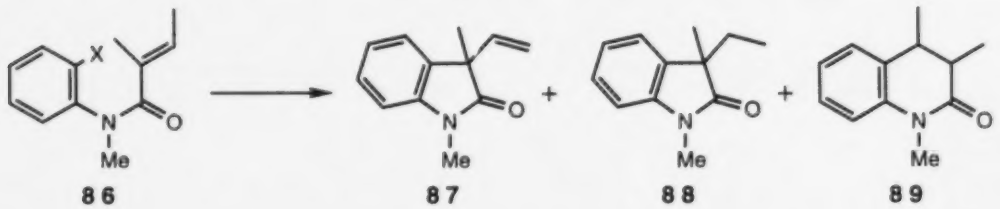
Scheme 29

Likewise, the radicals generated from *o*-bromo-*N*-propargyl anilides cyclize to give mixtures of indole products (Scheme 30).[46]



Scheme 30

Cobalt-mediated radical cyclization can also be applied to the closure of these systems. Treatment of amides **86** with Co(salen) gives the products of 5-*exo* (**87** and **88**) and 6-*endo* (**89**) closure



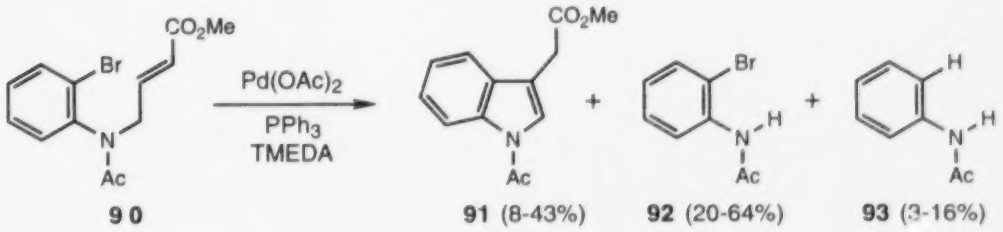
86 **87** **88** **89**

				5-*exo*	6-*endo*
X = I	Co(salen)	(66%)	72	2	26
X = Br	Co(salen)	(40%)	72	2	26
X = Br	Bu_3SnH	(65%)		72	28

Scheme 31

(Scheme 31).[47] Compound **87** is formed by β-elimination of the initially produced radical, while **88** and **89** are formed by hydrogen abstraction. For the purpose of comparison, the use of tributyltin hydride gives a similar ratio of 5-*exo* to 6-*endo* cyclization. Because of this similarity, a common intermediate is suggested for the two reagents, i.e. a free radical.

A related reaction, although not a radical process, is the palladium coupling of allyl anilides **90** (Scheme 32).[48] When treated with catalytic quantities of palladium acetate and triphenylphosphine, **90** gives modest yields of indole **91**, accompanied by the dealkylated amides **92** and **93**.



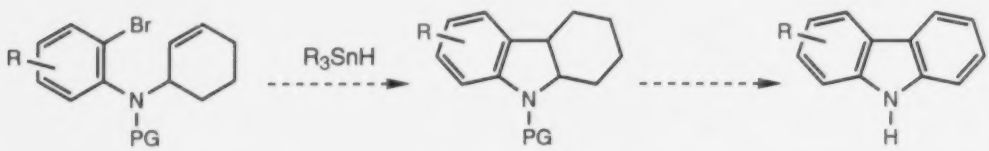
90 **91** (8-43%) **92** (20-64%) **93** (3-16%)

Scheme 32

In view of these reports, we were hopeful that our intended synthetic strategy would provide improved access to carbazoles such as the carbazomycins.

II DISCUSSION

Our strategy for the synthesis of carbazomycin B[49] involved the preparation of a suitably substituted and protected *ortho*-bromoaniline (Scheme 33), from which the aromatic radical could be generated. Radical cyclization to provide the hexahydrocarbazole, followed by deprotection and dehydrogenation should then generate the desired natural product.



Scheme 33

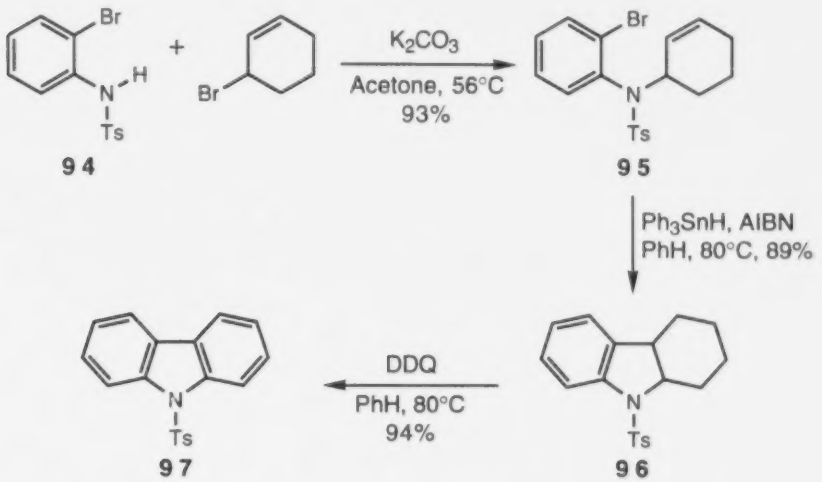
Model Studies

In order to test our approach, we began with a model study (Scheme 34).

The known sulfonamide **94**[50] was alkylated with 3-bromocyclohexene to give the cyclization precursor **95** in excellent yield. The *p*-toluenesulfonyl group was chosen as the protective group for nitrogen because of the ease of alkylating sulfonamides. We were unable to alkylate the corresponding *N*-benzyl derivative, and the *N*-acetyl derivative was alkylated in less than 50% yield.

Although the alkylated sulfonamide **95** appeared to be homogeneous by thin layer chromatography, its ^{1}H and ^{13}C NMR spectra indicated that it exists as a mixture of conformational diastereomers (which will be discussed later), in a four to one ratio.

However, both elemental analysis and high resolution mass spectroscopy showed the material to have the required composition.



Scheme 34

The isomer mixture was subjected to standard radical cyclization conditions and the desired cyclization product **96** was formed in high yield as a homogeneous substance, indicating that both isomers of the starting material had indeed been cyclized to the same product. Dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gave the protected carbazole **97**.[51]

This model suggested that our approach provided a high-yielding, direct route to carbazoles, and so we hoped to achieve an efficient synthesis of carbazomycin B.

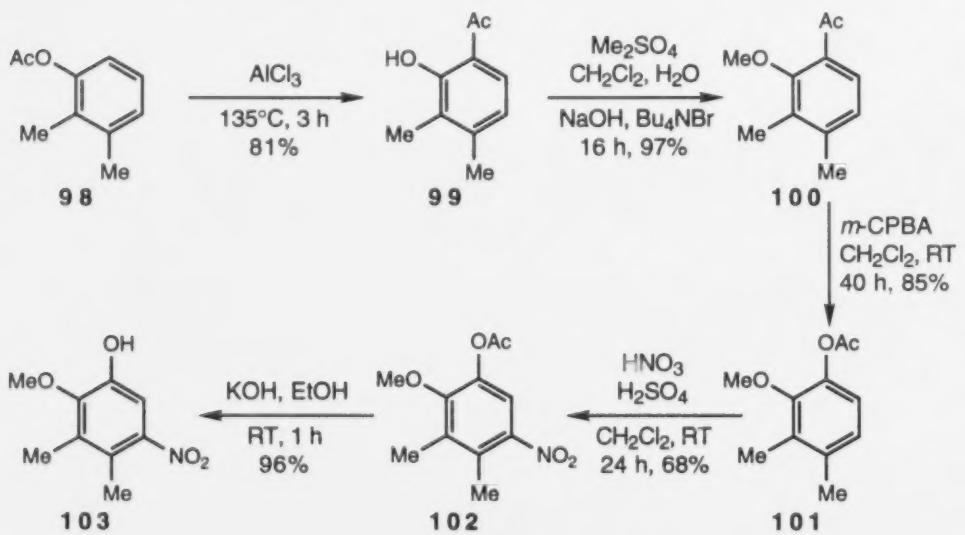
Preparation of Cyclization Precursors

We next considered the preparation of the fully substituted cyclization precursor.

In Knölker's synthesis of carbazomycin B,[44] the preparation of intermediate **103** (Scheme 35) is described, but without experimental details. Since the compound appeared to be a useful intermediate for our synthesis, we prepared it, using a variation of Knölker's methodology.

Fries reaction of the protected phenol **98**[52] gave a good yield of the desired acetophenone **99**.[53] The free phenol of **99** was protected with dimethyl sulfate under phase transfer conditions in near-quantitative yield.

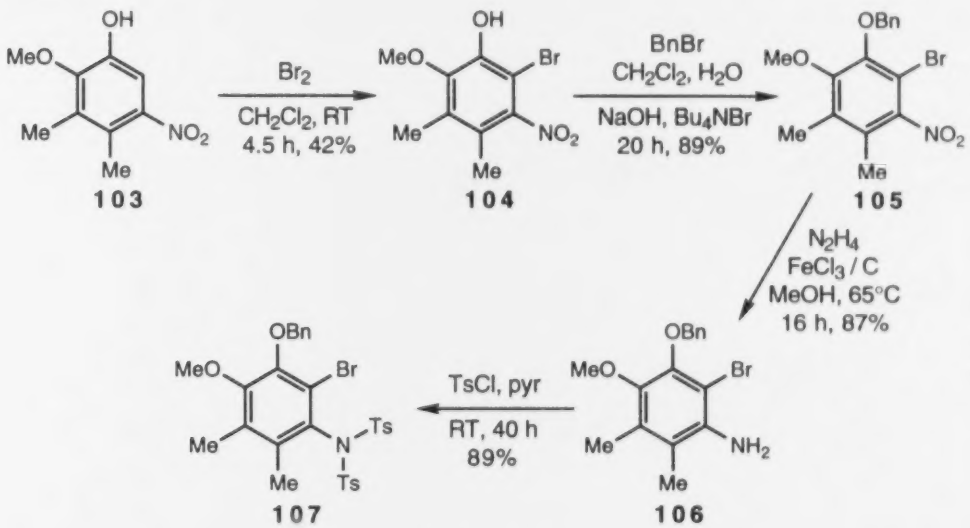
Baeyer-Villiger reaction of **100**[44a] gave the aromatic ester **101**,[44a] which was treated with nitric acid and a catalytic amount of sulfuric acid to produce the nitration product **102**.[44a] This material could be obtained pure in 68% yield, but for some purposes, better overall yields were obtained if it was used crude.



Scheme 35

Hydrolysis of the pure nitration product gave a quantitative yield of the desired intermediate **103**.[44a]

Bromination of **103** proved to be problematic, giving only a 42% yield of the unstable phenol **104** (Scheme 36). Nevertheless, **104** was benzylated under phase transfer conditions, and the resulting nitrate, **105**, was reduced to aniline **106**, using hydrazine hydrate and ferric chloride on activated carbon as catalyst.[54]



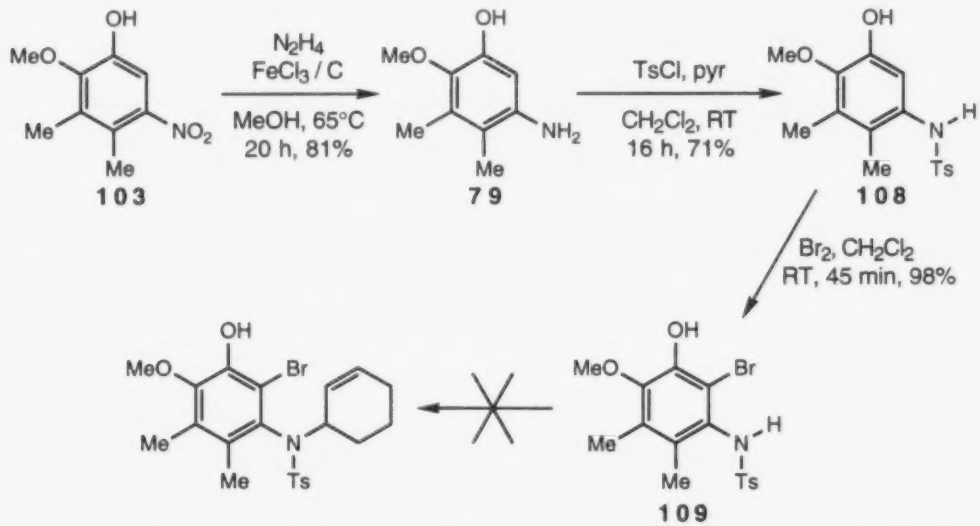
Scheme 36

When we attempted to tosylate **106**, the reaction appeared to progress very slowly, with only about 50% conversion of the starting material. After addition of an excess of *p*-toluenesulfonyl chloride, the reaction proceeded nearly to completion. Unlike the sulfonamide **95** in the model study (Scheme 34), the product was more polar (TLC) than the starting material and, surprisingly, it was not base-soluble, as would be expected of a secondary sulfonamide.

The material was identified as the tertiary sulfonimide **107**. None of the monoprotected material was observed by TLC or ^{1}H NMR.

In view of the low yield in the bromination step, this route was not investigated further.

After consideration of the above results, we thought that it may be necessary to reduce the nitro group prior to bromination. The nitrophenol **103**, which we had made previously, was reduced to aniline **79**[44b] (Scheme 37), again using hydrazine hydrate and ferric chloride.[54] This material could not easily be brominated, the resulting aminophenol being too water-soluble to isolate from the reaction mixture. Instead, **79** was selectively mono-protected to give sulfonamide **108**. This time, bromination gave a quantitative yield of the desired sulfonamide **109**. Unfortunately, this material could not be alkylated with 3-bromocyclohexene. All attempts to selectively protect the phenolic hydroxyl of **109** by esteri-

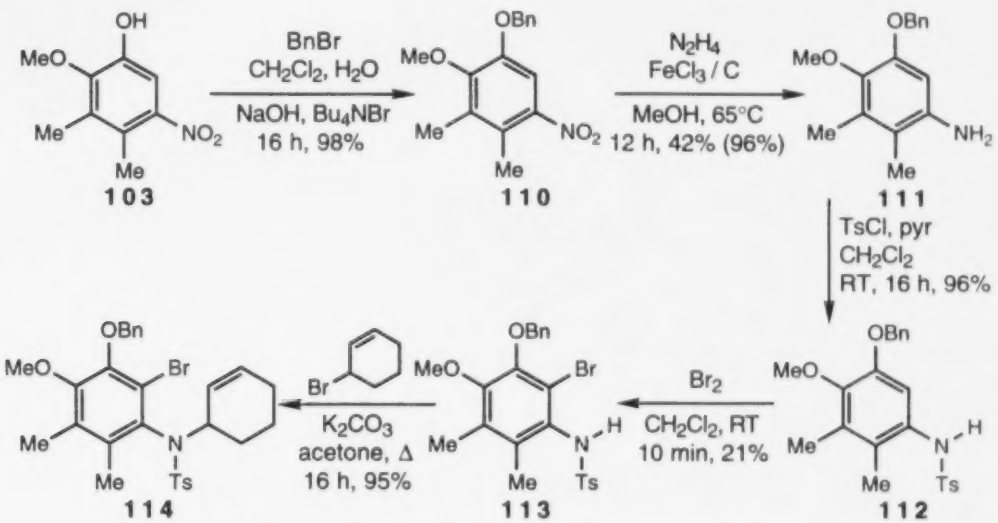


Scheme 37

fication, sulfonation, or silylation also failed – in all cases giving the *N,O*-di-protected derivatives.

In view of these results, we deemed it necessary to first protect the phenol, before reduction of the nitro group to the aniline.

The starting phenol **103** was protected, again as the benzyl ether (Scheme 38).



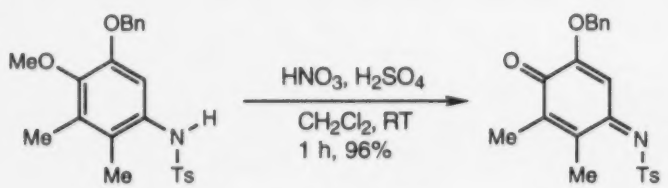
Scheme 38

Reduction of **110** under the same conditions as seen previously gave the desired aniline **111**, but this time, the reaction would not proceed beyond 42% conversion, although the yield was near-quantitative based on recovered starting material. Compound **111** could be converted in high yield to the desired sulfonamide **112**, with no trace of the disulfonation observed earlier (Scheme 36).

Once again, the bromination step proved to be problematic.

Treatment with bromine for ten minutes gave a dismal yield of the desired compound, accompanied by several other products, the major one being the debenzylated material (identical to authentic **108** prepared earlier). Numerous attempts at improving this yield, including the addition of various bases to neutralize the liberated HBr, and the addition of HBr acceptors, only gave poorer results. In some cases the *O*-methyl group appeared to be affected.

Therefore, we attempted to nitrate **112**, with the intention of generating the corresponding bromide by reduction of the nitro group, followed by Sandmeyer reaction. However, treatment with nitric acid, and a catalytic amount of sulfuric acid did not generate the required nitrate, but gave instead benzoquinone imine **115** (Scheme 39), the same compound observed in the attempted bromination of **112**. This result suggests that **112** may be too susceptible to oxidation to obtain a good yield in the bromination step.



112 **115**

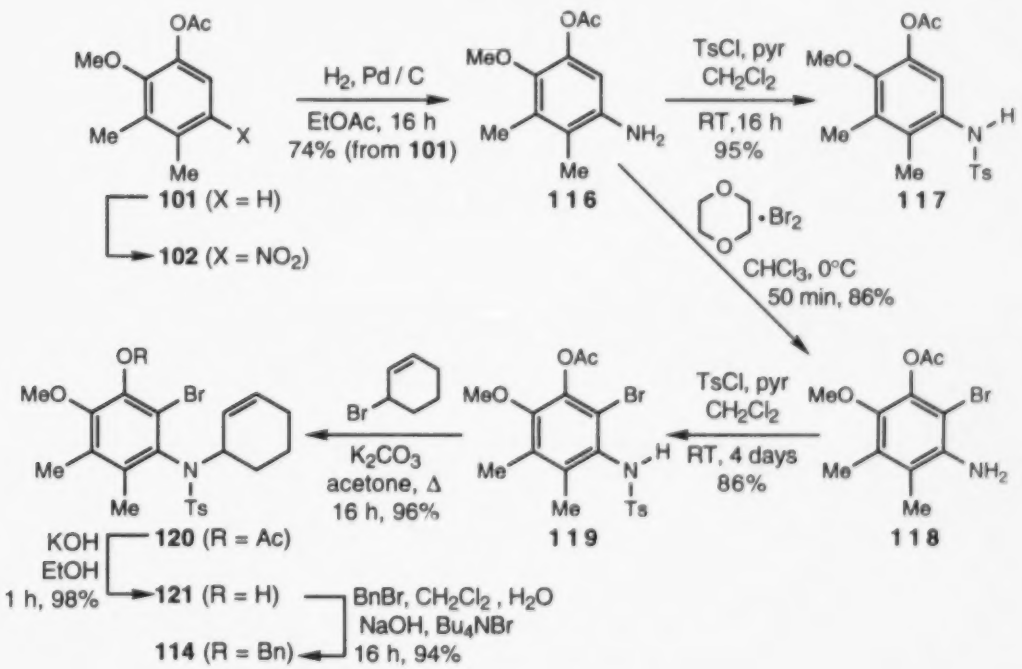
Scheme 39

Despite the low yield in the bromination step, the fully-substituted sulfonamide **113** was alkylated with 3-bromocyclohexene, to give the desired cyclization precursor **114**.

This material, like that in the model study, appeared to exist as a mixture of two isomers; however, this time they were separa-

ble by TLC, and we were able to separate a small amount of this material into the constituent isomers. The ^1H NMR spectra of the separate isomers were consistent with their being conformational diastereomers, as both compounds evidently had the same gross structure. Isomerism due to restricted rotation, or atropisomerism, is known to occur in highly congested systems.[55]

We still sought a more efficient route to **114**. The crude material from the nitration of **101** (seen in Scheme 35) was reduced by catalytic hydrogenation giving **116** in 74% yield for the two steps (Scheme 40). This material could be sulfonated, but the resulting sulfonamide **117** could not be brominated.



Scheme 40

Instead, **116** was brominated directly. Although use of

bromine in dichloromethane gave only a poor yield (less than 25%) of **118**, the major by-product being the de-acylated bromide, **116** could be brominated in very good yield using the bromine dioxane complex. Sulfonation of this material also proceeded cleanly to give **119**, again with no trace of the disulfonation observed earlier (Scheme 36).

Sulfonamide **119** was alkylated under similar conditions to those used earlier, to give **120**. Hydrolysis of the ester gave phenol **121**, which was converted to the benzyl ether **114**, seen previously.

All three of these compounds (**120**, **121** and **114**) exist as a mixture of isomers, and the ratio of these isomers appears to be constant throughout the sequence.

We now had three possible cyclization precursors with which to attempt the radical cyclization.

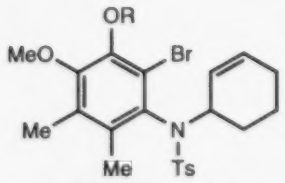
Radical Cyclizations

The radical cyclizations of **120**, **121** and **114** were performed under a variety of conditions, some of which are summarized in Table 1.

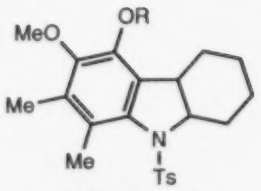
In these reactions, we observed the desired cyclization products (**122–124**, Table 1), along with the products of direct reduction (**125–127**), and also the unexpected fragmentation products (**117**, **108** and **112**) in which the cyclohexenyl ring had been cleaved, and the bromide reduced.

In the case of the *O*-acetyl derivative **120**, we were unable to

Table 1. Radical Cyclizations

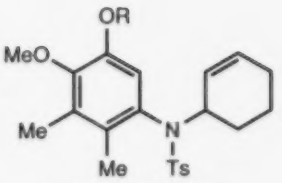


120 (R = Ac)
121 (R = H)
114 (R = Bn)



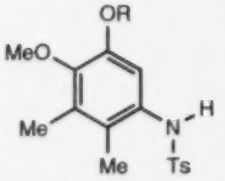
122 (R = Ac)
123 (R = H)
124 (R = Bn)

+



125 (R = Ac)
126 (R = H)
127 (R = Bn)

+



117 (R = Ac)
108 (R = H)
112 (R = Bn)

Precursor	Reaction Conditions[a]	Temperature (°C)	Cyclization Product (yield)	Direct Reduction (yield)	Fragmentation (yield)	Recovered Precursor (yield)
120 (R = Ac)	Method A[e]	80°C	**122** (35-40%)[b]	c	**117** (17%)	**120** (15%)[b]
	Method A[e]	111°C	**122** (29%)[b]	c	**117** (28%)	**120** (38%)[b]
	Method C[f]	0°C	**122** (34%)[b]	**125** (51%)[b]	c	d
	Method C[e]	5°C	**122** (46%)[b]	**125** (16%)[b]	c	**120** (17%)[b]
	Method C[e]	5°C	**123** (21%)[g]	**126** (25%)[g]	c	**121** (38%)[g]
	Method D	20°C	**122** (trace)	**125** (trace)	c	**120** (<18%)
121 (R = H)	Method A[e]	80°C	**123** (15%)	d	**108** (3%)	**121** (65%)
	Method B	20°C	**123** (18%)	**126** (5%)[b]	c	**121** (56%)
	Method C[e]	5°C	d	d	d	c
114 (R = Bn)	Method A[e]	80°C	**124** (39%)	**127** (14%)	**112** (9%)	d
	Method B	20°C	**124** (37-40%)	**127** (30%)	**112** (30%)	d
	Method C[e]	5°C	**124** (23%)[b]	**127** (28%)[b]	c	**114** (16%)[b]

a) Method A: Ph_3SnH, AIBN , refluxing benzene (80°C) or toluene (111°C). Method B: Ph_3SnH, Et_3B, O_2, benzene or hexanes. Method C: Ph_3SnH, AIBN, toluene, hv. Method D: SmI_2, HMPA, THF. b) NMR calculated yield. c)not determined. d) not observed. e) slow addition of Ph_3SnH and AIBN (double syringe pump). f) Ph_3SnH and AIBN added in one portion. g) after hydrolysis of the reaction mixture with KOH / EtOH.

separate the reaction products from one another or from unreacted starting material, and so many of the yields shown are based on ^{1}H NMR ratios.

Under usual radical cyclization conditions (slow addition of triphenyltin hydride and AIBN to a refluxing solution of **120** in benzene) the yield of cyclization product was about 35–40%. We also isolated 17% of the fragmentation product **117**, as well as some unreacted starting material. At higher temperature, the amount of fragmentation product increased.

Under photochemical conditions, the results appeared to be more promising. When triphenyltin hydride and AIBN were added slowly (16 hours by double syringe pump), the cyclization product appeared to be major by ^{1}H NMR. However, when the reaction mixture was hydrolyzed with ethanolic potassium hydroxide, the isolated yield of the cyclized material **123** was only 21%.

We also attempted to generate the aryl radical by reaction with samarium iodide. Little, if any, **123** was observed under these conditions (although in the model study, treatment of **95** by this method gave the cyclized material in approximately 40% yield).

Other, non-radical cyclization methods were also attempted. Palladium catalyzed coupling, for example, gave no reaction at all.

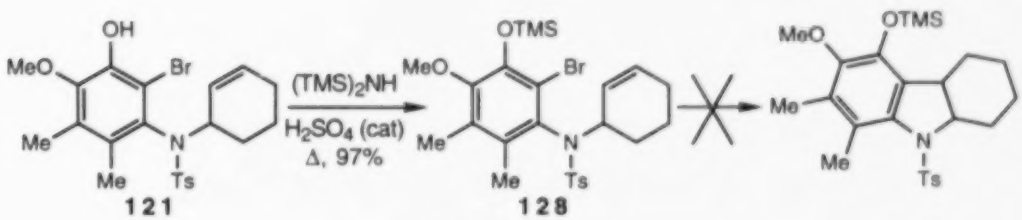
The cyclization of the unprotected phenol **121** proved to be even more problematic. Generation of the radical in this case was difficult, probably due to scavenging of the radicals by the phenol. The cyclized material was isolated in only 15–18% yield, whether AIBN or triethylborane was used as initiator. No reaction was

observed under photochemical conditions.

We had the most success using the *O*-benzyl protected material, **114**, in the cyclization. When driven to completion, the isolated yield of the desired compound was 37–40%. AIBN and triethylborane were equally effective in generating the radical. In these cases, the isolated yield of the fragmentation product **112** was up to 30%. Use of tributyltin hydride in place of triphenyltin hydride in the cyclizations gave no reaction.

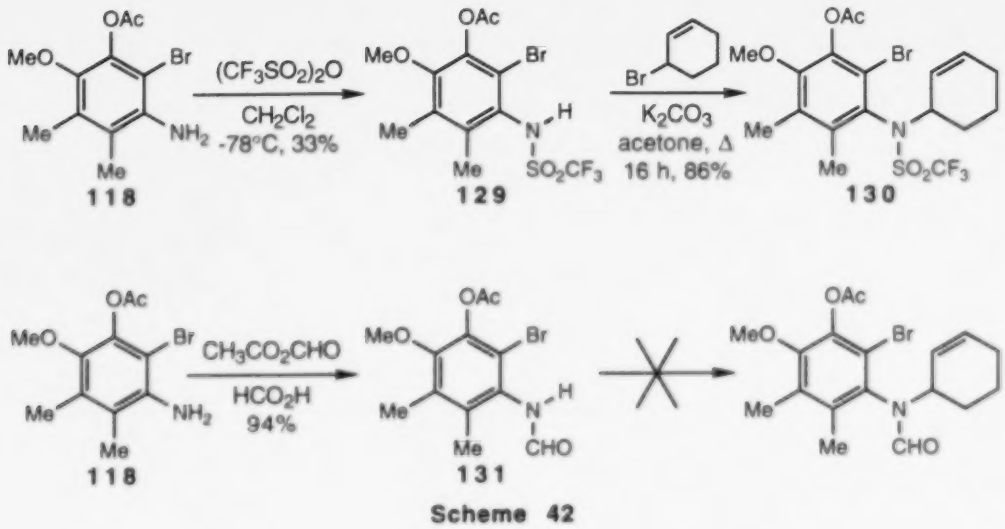
We also tried using other protective groups, hoping to avoid the formation of the undesired fragmentation.

We prepared the silyl protected phenol **128** (Scheme 41), but no cyclization product was observed under radical conditions.



Scheme 41

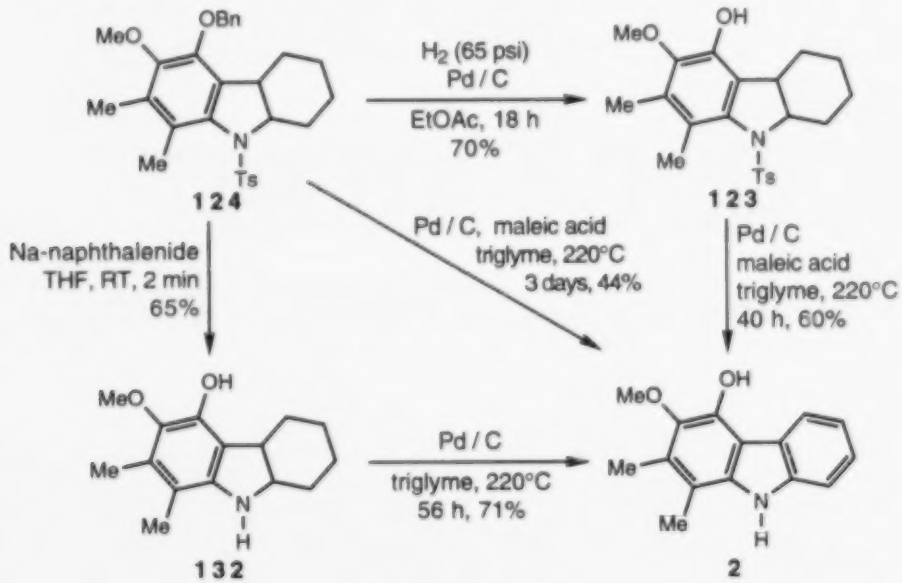
We also tried other forms of protection for the amino group (Scheme 42). The trifluoromethane sulfonamide **130** underwent the same type of fragmentation as the other sulfonamides, while the formamide **131** could not be alkylated under normal conditions.



Scheme 42

Completion of the Synthesis

The *o*-benzyl cyclization product **124** could be converted directly to carbazomycin B in 44% yield by heating to 220°C over palladium, using maleic acid as a hydrogen acceptor (Scheme 43).



Scheme 43

Evidently, some of the hydrogen liberated in the dehydrogenation serves to deprotect the sulfonamide and to debenzylate the phenol. Under milder conditions, or at lower temperatures, the reaction was exceedingly slow.

Alternatively, the debenzylated material **123**, available by hydrogenolysis of **124** or directly from the radical cyclization of **121**, could also be dehydrogenated in 60% yield.

More conveniently, sodium naphthalenide was used to deprotect both the sulfonamide and the benzyl ether to give a 65% yield of the unstable hexahydrocarbazole **132**. Dehydrogenation again gave **2**, this time in 71% yield. Our synthetic material had spectral characteristics (^{1}H and ^{13}C NMR) identical to those of natural carbazomycin B.[1b]

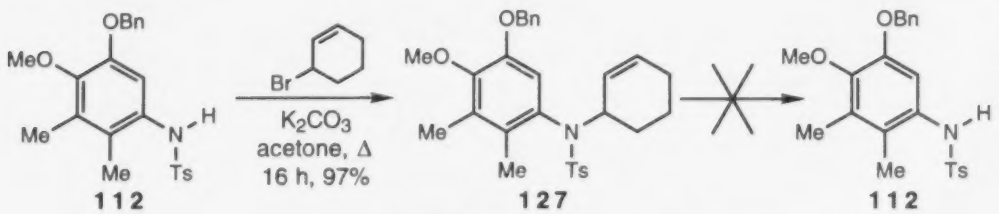
We also attempted to dehydrogenate **124** using DDQ, but the yield of the dehydrogenated material was very low (5–15%), the major by-products being the result of oxidation to a quinone or an iminoquinone.

Mechanistic Studies

In order to determine how the fragmentation product **112** (Table 1) is formed, we repeated the reduction of **114** using triphenyltin deuteride in place of triphenyltin hydride, and triethylborane as initiator. Under these conditions, we isolated 16% of **112**, with *no* incorporation of deuterium on the aromatic ring, a clear indication that the aromatic radical is not directly reduced by the tin reagent, but must abstract a hydrogen elsewhere, either inter-

or intramolecularly.

We also prepared the non-brominated analogue of **114** by alkylation of **112** (Scheme 44). When **127** was subjected to radical cyclization conditions, some decomposition of the starting material was evident, but no fragmentation product was formed. Clearly the fragmentation was not caused simply by addition of tin radicals to the double bond of **114** and expulsion of the sulfonamide fragment.



Scheme 44

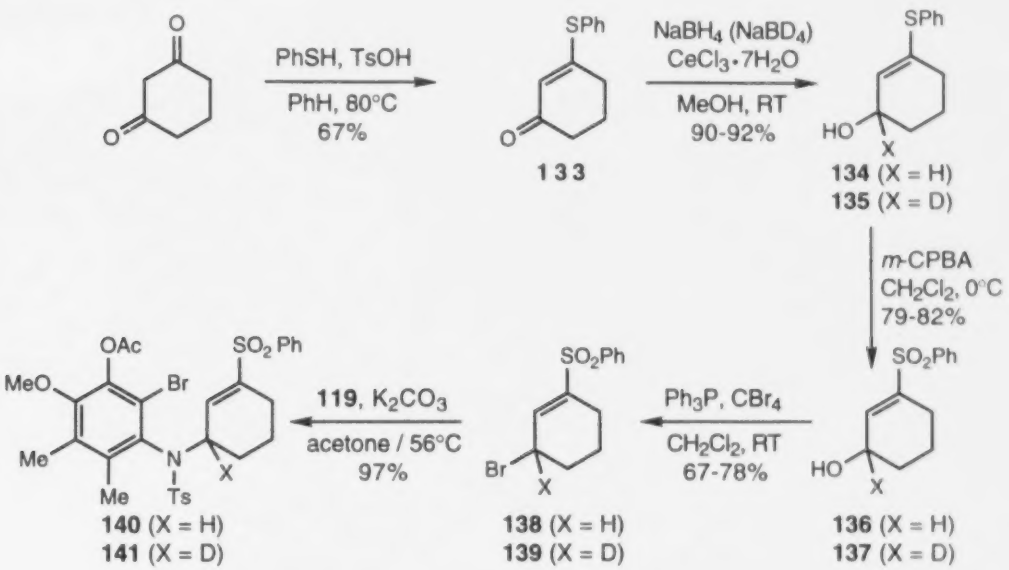
To determine if the fragmentation is a thermal process, a benzene solution of **114** was refluxed overnight – thermal conditions that resemble those used for the radical cyclization – and no decomposition was observed.

So far, all evidence indicated that the fragmentation is a radical process, likely involving abstraction of a hydrogen radical from the cyclohexenyl ring.

In order to further investigate this possibility, and in the hope of speeding up the radical cyclization (relative to other processes) by making the double bond electron deficient, we prepared the sulfones **140** (Scheme 45).

Following the literature procedure,[56] 1,3-cyclohexanedione was converted to sulfone **136**. By an analogous procedure, the

deuterated alcohol **137** was also prepared. The alcohols could be converted to the corresponding bromides **138** and **139** by treatment with triphenylphosphine and carbon tetrabromide.



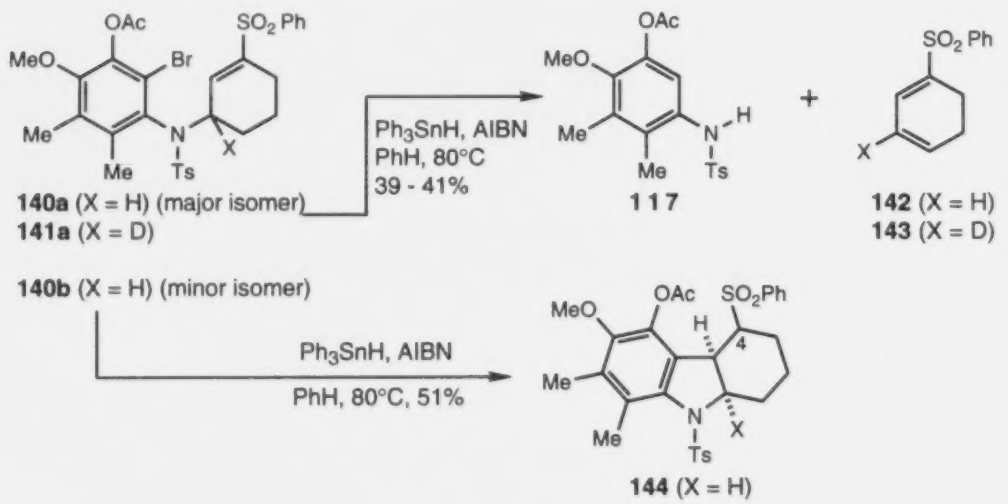
Scheme 45

The bromides were used to alkylate sulfonamide **119** to give the desired sulfones.

Once again, the sulfones **140** and **141** existed as a mixture of isomers. These isomers, however, were more easily separated than those previously encountered. We were able to obtain pure, crystalline samples of each isomer of **140** by careful flash chromatography and then recrystallization.

The separate isomers **140a** (major isomer) and **140b** (minor isomer) were each fully characterized, and both isomers appeared to be of the required composition.

We then subjected each isomer to the radical cyclization conditions (triphenyltin hydride and AIBN in refluxing benzene). The major isomer **140a** gave the fragmentation product **117** observed previously, and also a new product **142**,[57] each isolated in 40–41% yield (Scheme 46). No trace of the desired cyclization product was observed (^{1}H NMR).



Scheme 46

When the other isomer, **140b**, was subjected to the same conditions, the cyclization product **144** was formed in 51% yield, as a single isomer whose stereochemistry at C(4) was not established. No trace of the two fragmentation products was observed by TLC.

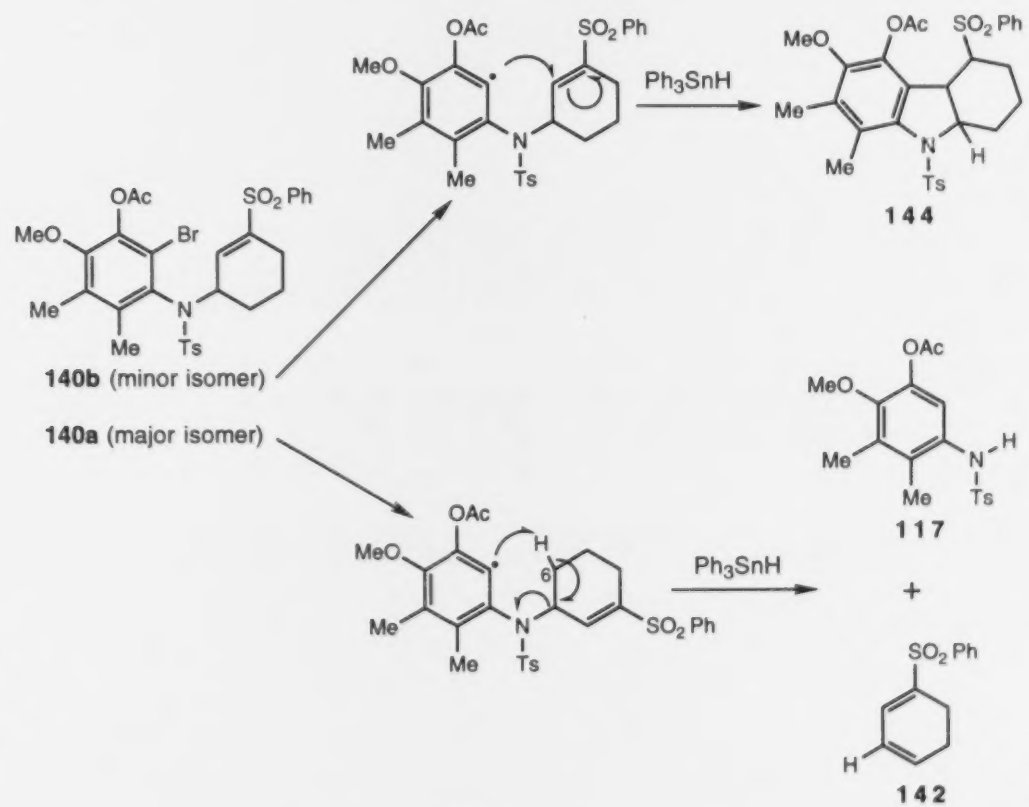
The reduction of the major isomer, **140a**, was repeated using triphenyltin deuteride in place of triphenyltin hydride. The two fragments **117** and **142** were isolated, each in 13–14% yield, but no deuterium incorporation was observed in either fragment.

The deuterium labelled sulfone **141** was prepared in order to

determine which hydrogen might be abstracted in the fragmentation process.

In this case, the minor isomer was not obtained pure. However, when the major isomer **141a** was subjected to the radical conditions, the deuterium was retained in the sulfone fragment **143**, and the sulfonamide fragment **117** had no deuterium incorporation. Clearly, it is not the allylic hydrogen which is abstracted in this process.

These observations led us to postulate the following mechanism (see Scheme 47). In the case of the minor isomer **140b**, the



Scheme 47

aromatic radical is generated from the bromide and, as usual, the radical cyclizes onto the double bond in a 5-*exo* closure to give, after reduction with triphenyltin hydride, the observed cyclization product **144**.

The radical generated from the major isomer **140a**, however, does not cyclize, but abstracts a hydrogen from C(6) of the cyclohexenyl ring. Elimination of the sulfonamide radical gives, after reduction, the two fragments **117** and **142**. Reduction using triphenyltin deuteride would place the deuterium on the sulfonamide nitrogen, where it would be subject to facile hydrogen exchange, thus accounting for the lack of deuterium incorporation in either fragment.

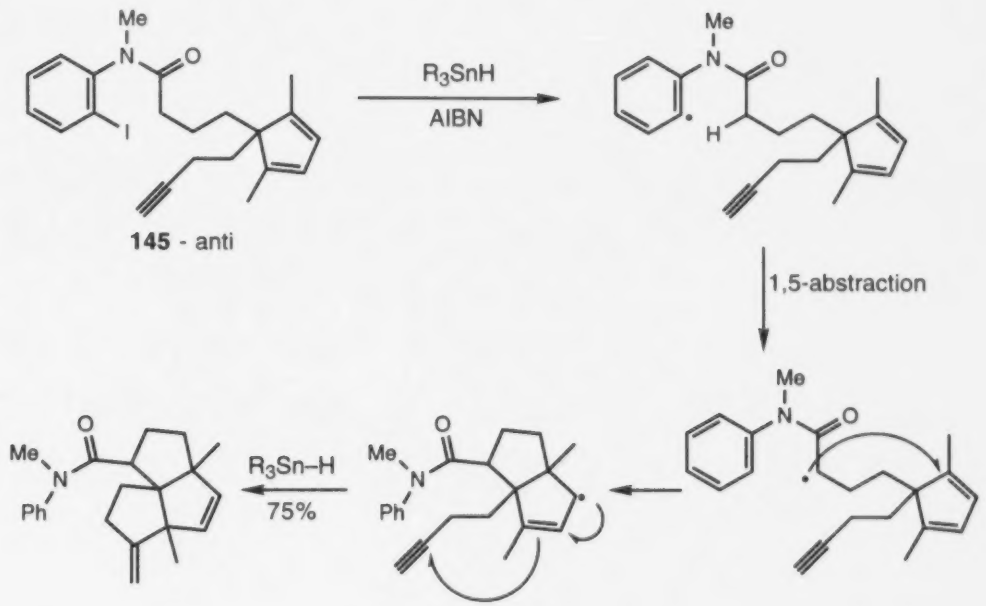
We did not think it worthwhile to perform further labelling experiments to confirm this mechanism, due to the difficulty in labelling the C(6) position without deuterium scrambling.

Intramolecular hydrogen abstractions, such as those postulated here, are not unknown, and several examples exist in the literature of similar observations.

Curran[58] has reported the generation of α-acyl radicals by 1,5-radical translocation from aryl radicals. These newly created radicals then cyclize onto double bonds within the molecule. Scheme 48 shows a particularly interesting example of this reaction.

It is felt that a critical factor in the success of this reaction is that there is a favorable anti rotamer population, because the radical derived from the syn isomer of **145** would not be able to ab-

stract the hydrogen, and the radical does not live long enough to rotate.

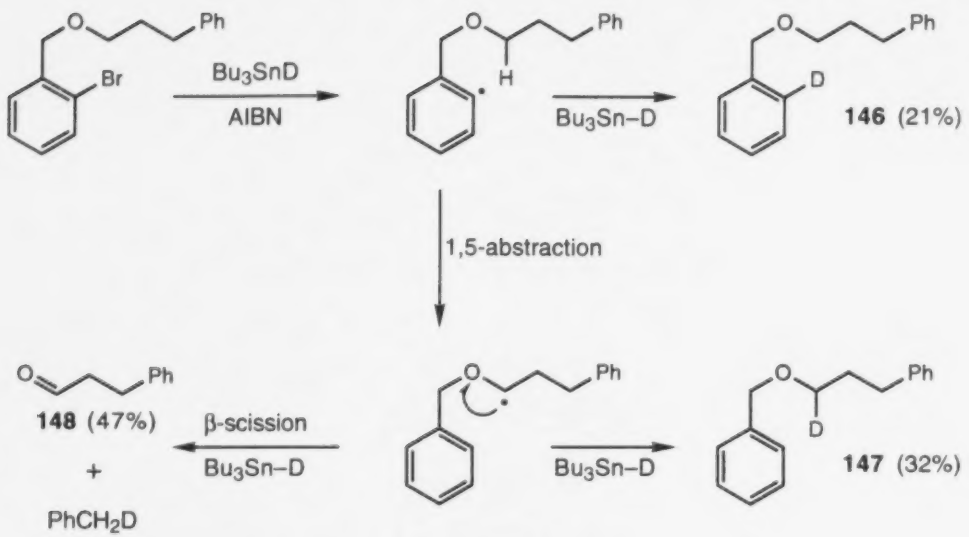


145 - anti

Scheme 48

In another report, De Mesmaeker[59] has detailed a similar 1,5-radical translocation of radicals generated from *o*-bromo benzylic ethers (Scheme 49). The use of tributyltin deuteride in the reduction allowed the determination of the extent of radical translocation. Interestingly, along with the reduced ethers **146** and **147**, aldehyde **148** was observed. It was proposed that **148** is formed by β-scission of the translocated radical. The aldehyde was isolated by in-situ olefination with $Ph_3P{=}CHCO_2Me$.

Similar 1,5-hydrogen abstractions have also been shown to occur in the corresponding sulfur, nitrogen and carbon compounds, however these derivatives do not give the products of β-scission.[59]



Scheme 49

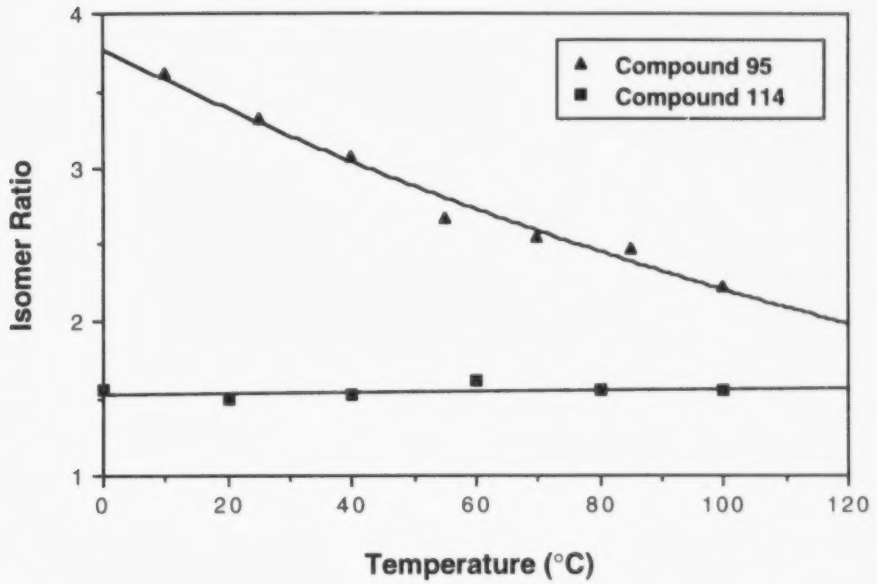
The formation of aldehyde **148** bears an interesting resemblance to our results, in that it appears to be formed by a process similar to that which we propose for the formation of the fragmentation products **117** and **142** (Scheme 47).

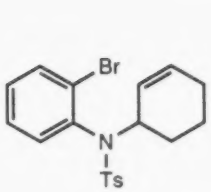
Origin of the Isomerism

The mechanism proposed above for the fragmentation and cyclization reactions (Scheme 47) presumes the existence of two diastereomers which differ only in conformation. In order for these two isomers to react in completely different manners, as they appear to from our results, interconversion between these isomers, and between the radicals derived from them, must be significantly slower than the cyclization and fragmentation reactions.

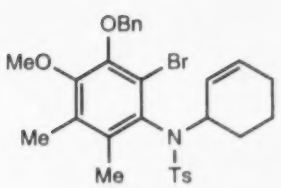
In order to test if these isomers are indeed interconverting, we first performed variable temperature ^1H NMR (C_7D_7, 400 MHz)

Figure 1. Isomer Ratio versus Temperature for Compounds 95 & 114





95



114

on two of our isomer mixtures. Spectra for compounds **95** and **114** were recorded over a temperature range of 0–100°C. Isomer ratios were determined from the NMR spectra by comparison of the integrals for the allylic and/or vinylic protons. Figure 1 shows the dependence of the ratio of isomers on temperature.

Although the NMR spectra of these compounds did not demonstrate a tendency to coalesce at higher temperatures, an interesting difference was observed in the behavior of the two compounds.

For compound **114**, no change in isomer ratio is observed over a range of 100°C. Compound **95**, however, shows a marked change in isomer ratio over the same temperature range and, although the signals do not coalesce, they do tend towards each other at higher temperature.

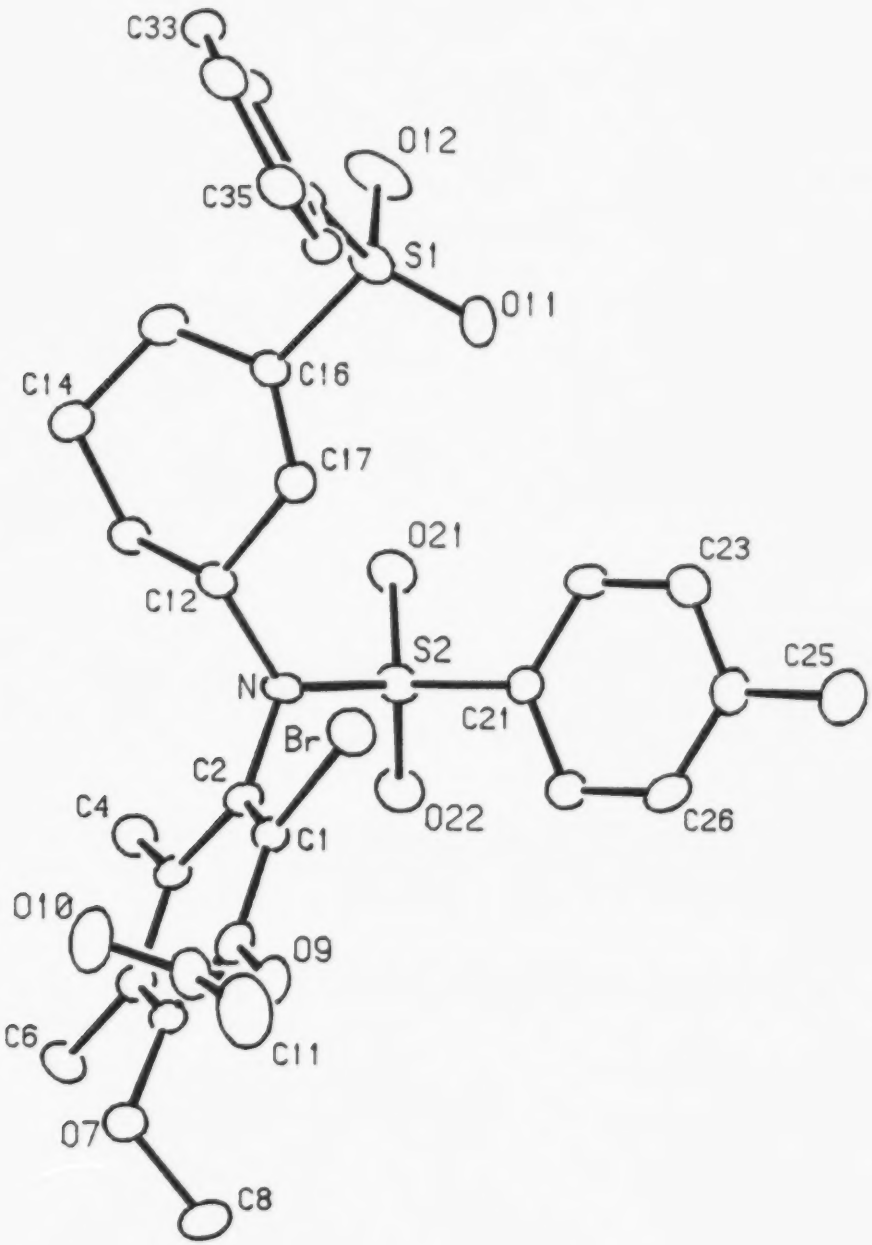
This result seems to indicate that the isomers of **95** are in equilibrium, and that the position of this equilibrium is temperature dependant.

The ratio of isomers of **114**, however, does not show any temperature dependence, so the barrier to interconversion between the isomers must be much higher.

In order to better understand the origin of these isomers, we examined more closely the separated isomers of sulfone **140**.

When individual samples of **140a** and **140b** are heated overnight in benzene (thermal conditions that resemble those used for the radical cyclizations) no interconversion is observed (^{1}H NMR, 200 MHz). The compounds also do not fragment under these

Figure 2. X-Ray Crystal Structure for Compound 140a



conditions.

Figure 2 shows the X-ray structure[60] of the major isomer **140a**. This structure confirms that **140a** is indeed a conformational diastereomer of the desired compound, but does not provide any obvious explanations for its failure to cyclize.

Unfortunately, the crystals of the minor isomer 140b were not suitable for X-ray analysis, and so we were unable to compare the structures in order to gain further insight into their different reactivities.

We did, however, arrange for molecular modelling and force-field calculations for the two isomers of **140** to be carried out.[61]

The X-ray crystal data for the major isomer were taken as the starting point and subjected to energy minimization. The resulting structure (Figure 3[62]) was very close to the X-ray structure, except for the orientation of the phenylsulfonyl group. This structure was found to be the most stable of all the rotational diastereomers.

Rings A and C were rotated 180° about their C-N bonds and the resulting structure was subjected to energy minimization, to produce a second conformer (Figure 4[62]) about 3 kcal/mole less stable than that of Figure 3.

Although molecular mechanics calculations cannot provide an exact value for the rotational energy barrier between the two isomers, this barrier was estimated to be very high. In fact, because of the steric bulk of the substituents on rings A and C, only a few stable conformations of **140** exist, all separated by high energy barriers.

Figure 3. Calculated Minimum Energy Conformation for Major Isomer of Compound 140[62]

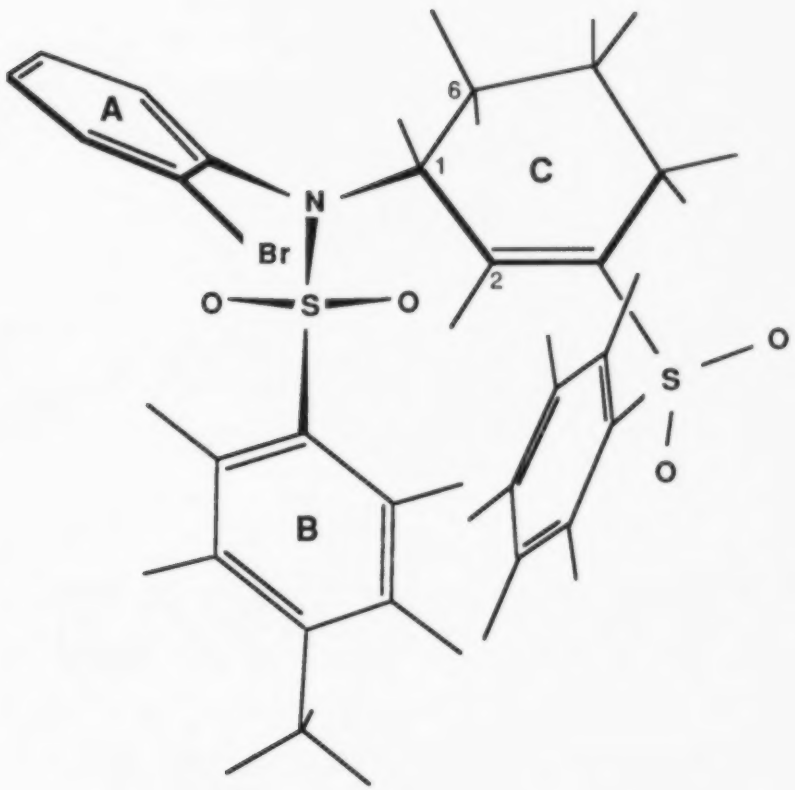
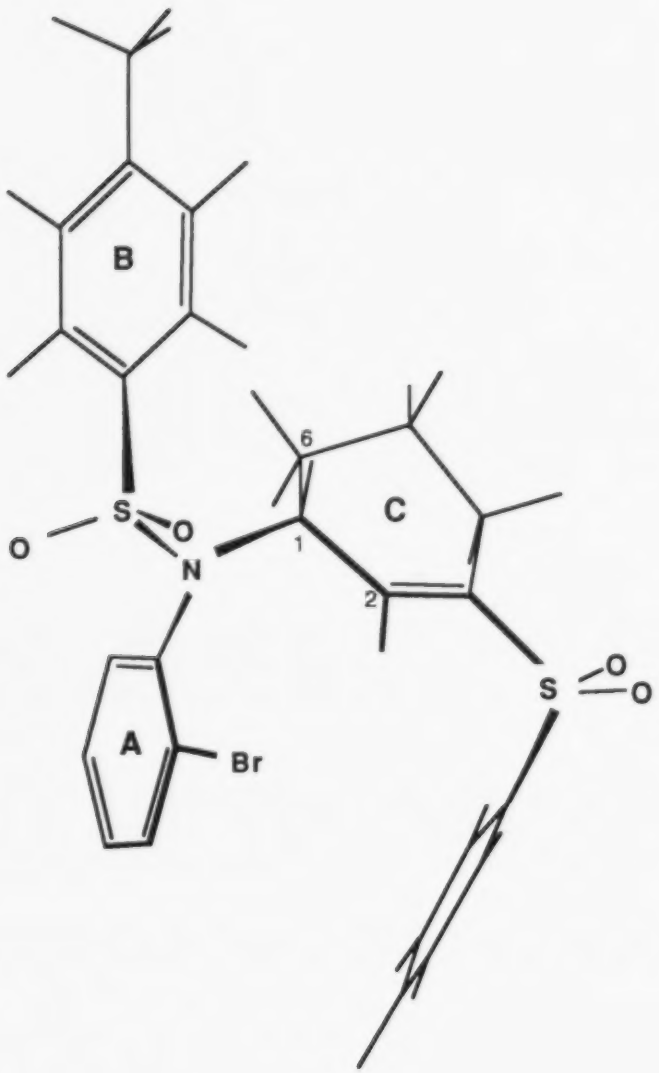


Figure 4. Calculated Minimum Energy Conformation for Second Isomer of Compound 140[62]



Although we cannot confirm that the calculated structure shown in Figure 4 is that of the minor isomer **140b**, it seems reasonable to propose that **140b** has a conformation similar to that of Figure 4, since it was the only other low-energy conformation identified for **140**.

Molecular dynamics calculations for both isomers showed no interconversion between the two isomers, consistent with the experimental fact that **140a** and **140b** do not interconvert under thermal conditions.

In order to explain why the two isomers of **140** react according to different pathways, we built CPK models of the radicals derived from the minimum energy conformations identified for the bromides, and the following observations were made:

In the case of the radical derived from the major isomer of **140**, there is no serious impediment to rotation about the N-C(1) bond (Figure 3), but rotation about the other bonds to the N is strongly hindered. Rotation about the N-C(1) bond alone does not convert the major isomer into the other identified isomer (Figure 4). In no accessible conformation is the radical suitably oriented[63] to attack the carbon-carbon double bond of ring C, however, it can approach the C(6) (Figure 3) hydrogens, one of which, we have suggested, is abstracted in the formation of **117** and **142**.

In the case of the radical derived from the other minimum energy conformation of **140**, rotation about the N-C(1) bond (Figure 4) appears to be much more restricted than for the corresponding bond of the major isomer, and approach to the C(6) hydrogens is

strongly hindered. However, the radical, without significant change in conformation from that of its parent bromide, is suitably placed to attack the carbon-carbon double bond of ring C following the preferred trajectory for the addition of a radical to a double bond, in which the attacking radical is in the plane of the pi orbitals, and approaches the C-C double bond at an angle of approximately 120° (Scheme 50).[63]

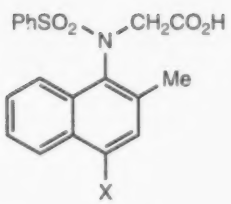
Scheme 50

The above analysis suggests that the difference in behavior of the isomeric bromides **140a** and **140b** is due to two factors – the energy barrier between the two isomers is too high for interconversion, and in the major isomer **140a**, the radical cannot easily approach the ring C double bond, but it can approach the C(6) hydrogens, while in the other isomer **140b**, the reverse is true.

The exceptionally high barrier to interconversion between the conformational diastereomers of **140**, while unusual, is not unprecedented. In fact, sulfonamides and amides account for many of the examples of atropisomerism encountered so far.[55]

In an extensive study of the sulfonamides **149**,[64] the enantiomers were prepared and resolved by their cinchonine esters, and their half-lives for racemization were measured by loss of optical

activity. It is found that electron-withdrawing groups in the para position speed up racemization, while electron donating groups have the opposite effect. Since the substituents do not have a significant steric influence on the center being racemized, this effect must be electronic in nature.



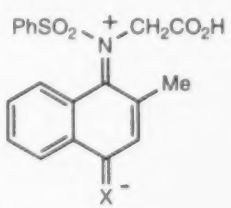
149

Table 2. $t_{1/2}$ for Racemization of Sulfonamides 149

X	$t_{1/2}$(h)*	X	$t_{1/2}$(h)*
NO_2	0.42	$NHSO_2Ph$	3.8
CN	0.62	$NHCOCH_3$	5.0
Br	3.7	NHCOPh	5.9
Cl	3.8	OCH_3	8.0
I	4.4	OH	8.7
H	4.9	NH_2	9.7
Me	5.5		

**half-life in DMF at 118°C*

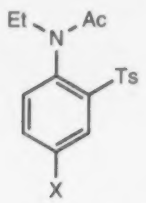
It has been suggested that the electron-withdrawing groups help to stabilize the planar transition state, **150**, thereby lowering the barrier to rotation about the C-N bond. Electron donating substituents would conversely destabilize the transition state.



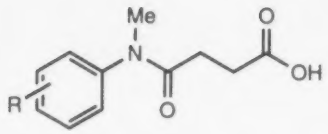
150

Similar effects have been observed for the optically active amides **151**,[65] which were resolved by crystallization from an

optically active solvent, and **152**.[66]



151



152

The isomers observed in our cyclization precursors likely result from a similar effect. The fact that **95** appears to be in equilibrium, while the isomers of the other compounds are shown not to interconvert, even at elevated temperatures, is likely a result of two factors – the increased steric strain imposed by the substituents on the aromatic ring, and the destabilization of the planar transition state by the electron-donating methoxy group para to the sulfonamide.

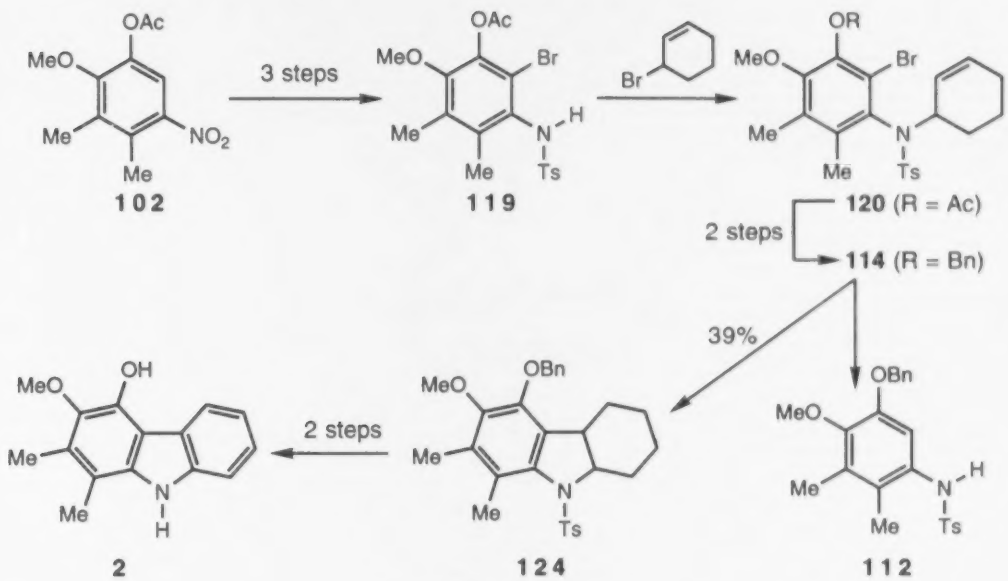
Conclusion

Although the use of radical cyclization has proved to be an effective tool for the formation of carbazoles in simple systems, the methodology has demonstrated some limitations in highly restricted systems.

We have been able to prepare carbazomycin B by our intended strategy, as summarized in Scheme 51.

Despite the disappointingly low yield in the cyclization step, our route has proved similar in scope to those already published.[42,44] Such highly substituted carbazole systems still remain a

synthetic challenge.



Scheme 51

III EXPERIMENTAL

General Procedures

Unless stated to the contrary, the following particulars apply: Reactions involving water- and air-sensitive reagents were done under argon, purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[67] and then through a similar column of Drierite. Glassware was dried in an oven for at least 2 h (120°C), cooled in a desiccator, assembled quickly, and sealed with rubber septa (when applicable). An inlet needle for argon was passed through a septum on the apparatus, which was then kept under a static pressure of argon. Stirring was effected by using a dry Teflon-coated magnetic stirring bar.

Solvents were distilled before use for chromatography. Where required, solvents and reagents were dried with suitable drying agents and distilled under argon. Dry tetrahydrofuran, ether and benzene were distilled from sodium-benzophenone ketyl; dry acetone was distilled twice from calcium sulfate; pyridine was distilled from calcium hydride. Azobisisobutyronitrile (AIBN) from Eastman was stored at 5°C and used without further purification.

Products were isolated from solution by concentration under water pump vacuum at 25–35°C using a rotary evaporator. Where compounds were isolated by simple evaporation of their solutions, the residues were kept under vacuum (<0.1 mm) until of constant weight. Melting points were measured with a Kofler block melting point apparatus. Commercial silica (Merck 60F-254) thin layer

chromatography (TLC) plates were used. Silica gel for flash chromatography was Merck type 60 (230–400 mesh). TLC plates were examined under UV radiation (254 nm), treated with iodine vapour, and charred on a hotplate after being dipped in a solution of ammonium molybdate[68] or vanillin.[69] Combustion elemental analyses were performed in the microanalytical laboratories of the University of Alberta. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer or a Nicolet 7000 FT-IR model. Infrared spectra of liquids were run as neat films on potassium bromide plates, while those of solids were run as chloroform or dichloromethane casts on the same plates. Proton NMR spectra were recorded on Varian EM-360 (at 60 MHz), Bruker WP-80 (at 80 MHz), Bruker WH-200 (at 200 MHz), Bruker AM-300 (at 300 MHz), or Bruker WH-400 (at 400 MHz) spectrometers in the specified deuterated solvent with tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on Bruker WH-200 (at 50.3 MHz), Bruker AM-300 (at 75.5 MHz), or Bruker WH-400 (at 100.6 MHz) spectrometers in the specified deuterated solvent. The following abbreviations are used in the text: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were recorded on an A.E.I. MS50 mass spectrometer at an ionizing voltage of 70 EV.

General methods for radical cyclization

Method A: Triphenyltin hydride and AIBN, each in the specified solvent, were added over 10 h (double syringe pump) to a

refluxing solution of the substrate in the same solvent. After the indicated workup, the reaction mixture was generally examined for product composition (^{1}H NMR, 200 MHz) prior to attempted purification of the products.

Method B: Triethylborane (1.0 M in hexanes) was added to a stirred solution of triphenyltin hydride and the substrate in the specified solvent. Air was injected into the solution over 10 h (syringe pump). The product mixture was examined as above.

Method C: A solution of the substrate in the specified solvent was stirred under argon in a water-cooled vessel. Triphenyltin hydride and AIBN, each in the same solvent, were added over 10 h (double syringe pump) to the solution as it was irradiated with a sun lamp (CGE model RSM, 275 Watt, 110–125 V). The product mixture was examined as above.

Method D: Samarium iodide (0.1 M in THF)[70] and hexamethylphosphoramide (HMPA) were added to the substrate, and the solution was stirred at room temperature. After workup as described, the mixture was examined for product composition.

_N_-(2-Bromophenyl)-4-methylbenzenesulfonamide (94).[50]

94

The literature procedure was followed, but with some modifications. *p*-Toluenesulfonyl chloride (4.13 g, 21.7 mmol) and

pyridine (1.70 mL, 21.0 mmol) were added to a stirred solution of *o*-bromoaniline (3.31 g, 19.2 mmol) in CH_2Cl_2 (50 mL). After 16 h little starting material remained (TLC, silica, 10:1 hexanes–ethyl acetate). The mixture was washed with HCl (1.2 N), and extracted with aqueous NaOH (1 N). The aqueous phase was acidified with concentrated HCl, and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and evaporated to give **94** (5.40 g, 94%) as an off-white, homogeneous (TLC, silica, 10:1 hexanes–ethyl acetate) solid: mp 94°C [lit.[50] mp 94–95°C]; FT-IR ($CHCl_3$ cast) 3270, 1479, 1337, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.36 (s, 3 H), 6.89–6.99 (m, 2 H), 7.16–7.29 (m, 3 H), 7.38 (dd, J = 1.5, 8 Hz, 1 H), 7.62–7.68 (m, 3 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.55, 115.72, 122.55, 126.26, 127.31, 128.54, 129.64, 132.58, 134.72, 135.89, 144.21; exact mass, m/z calcd for $C_{13}H_{12}{}^{81}BrNO_2S$ 326.9752, found 326.9751. Anal. Calcd for $C_{13}H_{12}BrNO_2S$: C, 47.87; H, 3.71; N, 4.29; O, 9.81; S, 9.83. Found: C, 47.74; H, 3.57; N, 4.18; O, 9.76; S, 9.75.

_N_-(2-Bromophenyl)-_N_-(2-cyclohexenyl)-4-methylbenzenesulfonamide (95).

94 **95**

A general method for alkylation was followed.[71] 3-Bromocyclohexene[72] (2.00 mL, 17.3 mmol) was added to a stirred mixture of **94** (4.8219 g, 14.8 mmol) and anhydrous K_2CO_3

(3.4698 g, 25.1 mmol) in anhydrous acetone (50 mL). The mixture was refluxed under argon for 16 h and evaporated. The residue was partitioned between ether and H_2O, and the aqueous phase was extracted with ether. The combined organic extracts were washed with aqueous NaOH (2.5 N), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **95** (5.58 g, 93%) as an apparently homogeneous (TLC, silica, 10:1 hexanes–ethyl acetate) white solid: mp 126–127°C; FT-IR ($CHCl_3$ cast) 1470, 1348, 1182 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.3–1.6 (m, 3 H), 1.7–1.9 (m, 2.2 H), 2.1–2.25 (m, 0.8 H), 2.45 (two s, 3 H), 4.85 (m, 1 H), 5.38 (m, 0.8 H), 5.68 (m, 1 H), 6.0 (m, 0.2 H), 7.0–7.1 (m, 1 H), 7.2–7.4 (m, 3 H), 7.65–7.75 (m, 3 H); Variable Temperature ^1H NMR (C_7D_7, 400 MHz) 10°C: δ 1.17–1.56 (m, 5 H), 1.87 (m, 0.22 H), 1.94 (s, 3 H), 2.11–2.19 (m, 0.78 H), 5.04 (m, 1 H), 5.48 (m, 1 H), 5.63 (m, 0.78 H), 6.23 (m, 0.22 H), 6.68 (m, 1 H), 6.79 (d, J = 4 Hz, 2 H), 6.84 (t, J = 4 Hz, 1 H), 7.13 (m, 1 H), 7.32 (d, J = 4 Hz, 0.22 H), 7.38 (d, J = 4 Hz, 0.78 H), 7.75 (t, J = 4 Hz, 2 H); 25°C: δ 1.18–1.60 (m, 5 H), 1.91 (m, 0.23 H), 1.96 (s, 3 H), 2.12 (m, 0.77 H), 5.00 (m, 1 H), 5.49 (m, 1 H), 5.67 (m, 0.77 H), 6.19 (m, 0.23 H), 6.69 (m, 1 H), 6.80 (d, J = 4 Hz, 2 H), 6.86 (t, J = 4 Hz, 1 H), 7.16 (m, 1 H), 7.33 (d, J = 4 Hz, 0.23 H), 7.39 (d, J = 4 Hz, 0.77 H), 7.72 (t, J = 4 Hz, 2 H); 40°C: δ 1.20–1.62 (m, 5 H), 1.92 (m, 0.24 H), 1.97 (s, 3 H), 2.12 (m, 0.76 H), 4.98 (m, 1 H), 5.50 (m, 1 H), 5.68 (m, 0.76 H), 6.18 (m, 0.24 H), 6.69 (m, 1 H), 6.90–6.77 (m, 3 H), 7.17 (m, 1 H), 7.34 (d, J = 4 Hz, 0.24 H), 7.39 (d, J = 4 Hz, 0.76 H), 7.72 (t, J = 4 Hz, 2 H); 55°C: δ 1.23–1.67

(m, 5 H), 1.95 (m, 0.27 H), 2.00 (s, 3 H), 2.10 (m, 0.73 H), 4.96 (m, 1 H), 5.52 (m, 1 H), 5.71 (m, 0.73 H), 6.17 (m, 0.27 H), 6.71 (m, 1 H), 6.79–6.91 (m, 3 H), 7.21 (m, 1 H), 7.34 (d, J = 4 Hz, 0.27 H), 7.40 (d, J = 4 Hz, 0.73 H), 7.74 (t, J = 4 Hz, 2 H); 70°C: δ 1.25–1.70 (m, 5 H), 1.95 (m, 0.28 H), 2.00 (s, 3 H), 2.10 (m, 0.72 H), 4.95 (m, 1 H), 5.55 (m, 1 H), 5.74 (m, 0.72 H), 6.15 (m, 0.28 H), 6.72 (m, 1 H), 6.80–6.92 (m, 3 H), 7.22 (m, 1 H), 7.35 (d, J = 4 Hz, 0.28 H), 7.40 (d, J = 4 Hz, 0.72 H), 7.73 (t, J = 4 Hz, 2 H); 85°C: δ 1.24–1.73 (m, 5 H), 1.96 (m, 0.29 H), 2.00 (s, 3 H), 2.08 (m, 0.71 H), 4.93 (m, 1 H), 5.56 (m, 1 H), 5.76 (m, 0.71 H), 6.14 (m, 0.29 H), 6.73 (m, 1 H), 6.80–6.94 (m, 3 H), 7.24 (m, 1 H), 7.35 (d, J = 4 Hz, 0.29 H), 7.39 (d, J = 4 Hz, 0.71 H), 7.70 (t, J = 4 Hz, 2 H); 100°C: δ 1.30–1.80 (m, 5 H), 2.01 (m, 0.31 H), 2.08 (s, 3 H), 2.13 (m, 0.69 H), 4.97 (m, 1 H), 5.61 (m, 1 H), 5.83 (m, 0.69 H), 6.16 (m, 0.31 H), 6.79 (m, 1 H), 6.88–7.00 (m, 3 H), 7.30 (m, 1 H), 7.40 (d, J = 4 Hz, 0.31 H), 7.45 (d, J = 4 Hz, 0.69 H), 7.78 (t, J = 4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.23, 21.57, 24.22, 28.00, 28.55, 57.90, 58.23, 127.26, 127.35, 127.44, 127.64, 127.89, 127.95, 128.59, 129.04, 129.42, 129.54, 129.82, 129.97, 130.86, 131.98, 132.82, 133.69, 133.91, 134.20, 136.13, 136.35, 138.21, 143.39, 143.44; exact mass, m/z calcd for $C_{19}H_{20}{}^{79}BrNO_2S$ 405.0398, found 405.0398. Anal. Calcd for $C_{19}H_{20}BrNO_2S$: C, 56.16; H, 4.96; N, 3.45; O, 7.87; S, 7.89. Found: C, 55.90; H, 5.04; N, 3.59; O, 7.95; S, 7.98. Both the ^{1}H and ^{13}C NMR spectra show that the material exists as a mixture of conformational isomers.

1,2,3,4,4a,9a-Hexahydro-9-[(4-methylphenyl)sulfonyl]-carbazole (96).

95 **96**

Method A: Triphenyltin hydride (0.25 mL, 0.979 mmol) in anhydrous benzene (10 mL) and AIBN (19.6 mg, 0.120 mmol) in benzene (10 mL) were added over 10 h (double syringe pump) to a refluxing solution of **95** (265.1 mg, 0.653 mmol) in the same solvent (40 mL). The solution was refluxed a further 6 h, cooled, and then stirred for several hours at room temperature with a saturated solution of aqueous KF. The aqueous phase was extracted with ether, and the combined organic extracts were washed with H_2O and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **96** (189.7 mg, 89%) as a white, homogeneous (TLC, silica, 10:1 hexanes–ethyl acetate) solid: mp 116°C; FT-IR ($CHCl_3$ cast) 1352, 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.0–2.25 (m, 2 H), 2.3–2.7 (m, 4 H), 2.95–3.10 (m, 2 H), 3.33 (s, 3 H), 3.84 (m, 1 H), 4.25 (dt, J = 10, 6 Hz, 1 H), 6.98–7.26 (m, 5 H), 7.54–7.64 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.67, 21.53, 22.44, 24.50, 29.16, 39.93, 63.61, 117.94, 123.07, 124.69, 126.73, 127.61, 129.60, 135.92, 136.80, 141.52, 143.57; exact mass, m/z calcd for $C_{19}H_{21}NO_2S$ 327.1293, found 327.1295. Anal. Calcd for $C_{19}H_{21}NO_2S$:

C, 69.69; H, 6.46; N, 4.28; O, 9.77; S, 9.79. Found: C, 69.78; H, 6.48; N, 4.48; O, 9.40; S, 9.97.

Method D: Samarium iodide (1.0 M in THF, 7.0 mL, 0.70 mmol) and dry HMPA (0.9 mL) were added to **95** (95.2 mg, 0.234 mmol), and the mixture stirred under argon at room temperature for 3.5 h. The solution was diluted with ether, washed with HCl (1.2 N) and then with saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave a mixture containing **96** (40% calculated yield, ^1H NMR, 200 MHz) and unreacted **95** (20% calculated yield), as well as several other unidentified products.

9-[(4-Methylphenyl)sulfonyl]carbazole (97).[51]

96 **97**

A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (117.4 mg, 0.517 mmol) and **96** (49.0 mg, 0.150 mmol) in benzene (12 mL) was refluxed under argon for 16 h and then evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **97** (45.4 mg, 94%) as a white, homogeneous (TLC, silica, 4:1 hexanes–ethyl acetate) crystalline solid: mp 129–130°C [lit.[51] mp 129–129.5°C]; FT-IR ($CHCl_3$ cast) 1441, 1370, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.20 (s, 3 H),

7.04 (d, J = 8 Hz, 2 H), 7.33 (t, J = 8 Hz, 2 H), 7.48 (td, J = 8, 2 Hz, 2 H), 7.68 (d, J = 9 Hz, 2 H), 7.87 (dd, J = 8, 2 Hz, 2 H), 8.33 (d, J = 9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.43, 115.14, 119.98, 123.88, 126.31, 126.44, 127.74, 129.61, 134.99, 138.39, 144.83; exact mass, m/z calcd for $C_{19}H_{15}NO_2S$ 321.0824, found 321.0820. Anal. Calcd for $C_{19}H_{15}NO_2S$: C, 71.01; H, 4.70; N, 4.36; S, 9.98. Found: C, 70.89; H, 4.61; N, 4.37; S, 9.70.

2-Hydroxy-3,4-dimethylacetophenone (99).[44a,53]

98 **99**

The literature method was followed, but with some modifications. Finely powdered, anhydrous aluminum chloride (53.27 g, 0.40 mol) and **98**[52] (27.78 g, 0.169 mol) in a 500 mL round-bottomed flask, equipped with an air condenser and calcium sulfate drying tube, were heated slowly over 0.5 h to 135°C and kept at this temperature for a further 3 h. The solution was cooled to 0°C, and ice was then added until evolution of HCl ceased. The solution was diluted with H_2O (300 mL) and extracted with CH_2Cl_2 (3 x 250 mL). The organic extract was washed with H_2O (200 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **99** (22.65 g, 81%) as a pale yellow, homogeneous (TLC, silica, 10:1 hexanes–ethyl

acetate) oil: FT-IR ($CHCl_3$ cast) 1631, 1322, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.18 (s, 3 H), 2.32 (s, 3 H), 2.61 (s, 3 H), 6.70 (d, J = 9 Hz, 1 H), 7.49 (d, J = 9 Hz, 1 H), 11.87 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 10.91, 20.70, 26.44, 117.23, 120.35, 125.34, 127.53, 146.06, 160.67, 204.15; exact mass, m/z calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0837. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.36; H, 7.54.

2-Methoxy-3,4-dimethylacetophenone (100).[44a]

99 **100**

This compound has been reported,[44a] but without experimental details. Ketone **99**[53] (5.27 g, 0.0321 mol) in CH_2Cl_2 (250 mL), aqueous NaOH (2.5 N, 200 mL), dimethyl sulphate (9.0 mL, 0.0951 mol) and tetrabutylammonium bromide (1.23 g, 0.0038 mol) were stirred vigorously for 16 h. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 75 mL). The combined organic extracts were washed with 25% v/v NH_4OH (3 x 300 mL), dried ($MgSO_4$), and evaporated. Flash chromatography over silica gel, using 4:1 hexanes–CH_2Cl_2, gave **100** (5.53 g, 97%) as a pale yellow, homogeneous (TLC, silica, 2:1 hexanes–CH_2Cl_2) oil: FT-IR ($CHCl_3$ cast) 1678, 1598, 1398, 1276 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.25 (s, 3 H), 2.32 (s, 3 H), 2.66 (s, 3 H), 3.77 (s, 3 H), 7.02

(d, J = 8 Hz, 1 H), 7.45 (d, J = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.99, 20.40, 30.31, 61.94, 125.47, 126.86, 130.59, 130.69, 143.32, 157.68, 200.41; exact mass, m/z calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0996. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.00; H, 7.78.

2-Methoxy-3,4-dimethylphenyl acetate (101).[44a]

100 **101**

This compound has been reported,[44a] but without experimental details. A solution of *m*-CPBA (70–80%, 20.61 g, 0.084–0.096 mol) and **100** (5.0265 g, 0.0282 mol) in CH_2Cl_2 (250 mL) was stirred in the dark under argon for 40 h. The stirred solution was cooled to 0°C and aqueous Na_2SO_3 (0.7 M, 150 mL) was added dropwise over 1.5 h. The organic layer was washed with saturated aqueous $NaHCO_3$ (3 x 300 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 4:1 hexanes–CH_2Cl_2, gave **101** (4.6995 g, 85%) as a yellow, homogeneous (TLC, silica, 1:1 hexanes–CH_2Cl_2) crystalline solid: mp 41–43°C; FT-IR ($CHCl_3$ cast) 1784, 1225, 1201 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.20 (s, 3 H), 2.21 (s, 3 H), 2.32 (s, 3 H), 3.74 (s, 3 H), 6.81 (d, J = 8 Hz, 1 H), 6.91 (d, J = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.35, 19.82, 20.74, 60.65, 119.77, 125.14, 131.17, 135.93, 141.77,

149.67, 169.35; exact mass, *m/z* calcd for $C_{11}H_{14}O_3$ 194.0942, found 194.0944. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.67; H, 7.41.

2-Methoxy-3,4-dimethyl-5-nitrophenyl acetate (102).[44a]

101 **102**

This compound has been reported,[44a] but without experimental details. Concentrated HNO_3 (5.0 mL, 0.078 mol) and then concentrated H_2SO_4 (10 drops) were added rapidly to a stirred solution of **101** (4.6172 g, 0.0238 mol) in CH_2Cl_2 (150 mL). After being stirred for 24 h, the solution was washed successively with H_2O (250 mL), saturated aqueous $NaHCO_3$ (2 x 250 mL), and brine (200 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **102** (3.89 g, 68%) as a pale yellow, homogeneous (TLC, silica, 5:1 hexanes–ethyl acetate) solid: mp 76–78°C; FT-IR ($CHCl_3$ cast) 1779, 1515, 1199, 1188 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.30 (s, 3 H), 2.37 (s, 3 H), 2.42 (s, 3 H), 3.82 (s, 3 H), 7.54 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.08, 15.85, 20.60, 60.94, 117.46, 131.10, 133.79, 141.07, 145.88, 153.43, 168.51; exact mass, *m/z* calcd for $C_{11}H_{13}NO_5$ 239.0794, found 239.0797. Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.28; H, 5.48; N, 5.89.

2-Methoxy-3,4-dimethyl-5-nitrophenol (103).[44a]

102 **103**

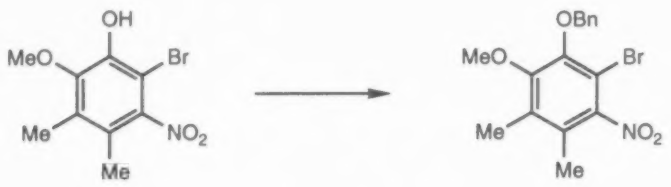
This compound has been reported,[44a] but without experimental details. A solution of **102** (3.83 g, 0.0160 mol) in ethanolic KOH (3.5% w/v, 280 mL) was stirred for 1 h and then the solvent was evaporated. The residue was taken up in H_2O (200 mL), acidified with HCl (1.2 N), and extracted with CH_2Cl_2 (3 x 200 mL). The organic extract was washed with HCl (1.2 N, 300 mL), and brine (300 mL), dried ($MgSO_4$) and evaporated to afford **103** (3.03 g, 96%) as a pale yellow, homogeneous (TLC, silica, 5:1 hexanes–ethyl acetate) crystalline solid: mp 60–61°C; FT-IR ($CHCl_3$ cast) 3450, 1529, 1480, 1338 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.30 (s, 3 H), 2.35 (s, 3 H), 3.85 (s, 3 H), 5.75 (br s, 1 H), 7.33 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.11, 15.16, 61.05, 109.18, 124.26, 131.96, 146.71, 146.96, 148.77; exact mass, *m/z* calcd for $C_9H_{11}NO_4$ 197.0688, found 197.0690. Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.99; H, 5.35; N, 7.17.

2-Bromo-6-methoxy-4,5-dimethyl-3-nitrophenol (104).

103 **104**

Bromine (0.30 mL, 5.9 mmol) in CH_2Cl_2 (3 mL) was added over 2 min to a stirred solution of **103** (727.2 mg, 3.69 mmol) in CH_2Cl_2 (50 mL). Stirring was continued in the dark for 90 min, but the reaction was still incomplete (TLC, silica, 5:1 hexanes–ethyl acetate). Bromine (1.4 mL, 27 mmol) was added, and the solution stirred in the dark a further 3 h, at which stage no **103** was apparent by TLC. The solution was washed with Na_2SO_3 (0.7 N), saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 5:1 hexanes–ethyl acetate, gave **104** (425.0 mg, 42%) as an unstable yellow, homogeneous (TLC, silica, 5:1 hexanes–ethyl acetate) solid: ^1H NMR ($CDCl_3$, 200 MHz) δ 2.18 (s, 3 H), 2.27 (s, 3 H), 3.88 (s, 3 H), 6.12 (s, 1 H). The material was used directly in the next step.

1-Bromo-3-methoxy-4,5-dimethyl-6-nitro-2-(phenylmethoxy)benzene (105).



104 **105**

A mixture of **104** (343.1 mg, 1.24 mmol) in CH_2Cl_2 (12 mL), aqueous NaOH (2.5 N, 5 mL), benzyl bromide (0.17 mL, 1.43 mmol), and tetrabutylammonium bromide (160.9 mg, 0.500 mmol) was stirred vigorously for 20 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **105** (405.3 mg, 89%) as a white, homogeneous (TLC, silica, 10:1 hexanes–ethyl acetate) solid: mp 108°C; FT-IR ($CHCl_3$ cast) 1532, 1379, 1363 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.20 (s, 3 H), 2.24 (s, 3 H), 3.87 (s, 3 H), 5.03 (s, 2 H), 7.35–7.50 (m, 3 H), 7.50–7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.73, 14.69, 60.93, 75.47, 106.34, 125.85, 128.51, 128.58, 132.45, 136.36, 148.04, 148.76, 153.33; exact mass, *m/z* calcd for $C_{16}H_{16}{}^{81}BrNO_4$ 367.0242, found 367.0248. Anal. Calcd for $C_{16}H_{16}BrNO_4$: C, 52.48; H,4.40; N, 3.82. Found: C, 52.66; H, 4.46; N, 3.79.

2-Bromo-4-methoxy-5,6-dimethyl-3-(phenylmethoxy)-aniline (106).[54]

105 **106**

Hydrazine hydrate (0.56 mL, 11.5 mmol) in MeOH (5 mL) was added over 2 h to a refluxing mixture of **105** (349.6 mg, 0.955 mmol), activated carbon (25.0 mg, 2.1 mmol), and $FeCl_3 \cdot 6H_2O$ (4.4 mg, 0.0162 mmol) in MeOH (12 mL). After being refluxed overnight, the solution was filtered through Celite and evaporated. The residue was partitioned between CH_2Cl_2 (15 mL) and NaOH (1 N, 15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic phases dried ($MgSO_4$), filtered through silica gel, and evaporated to give **106** (278.1 mg, 87%) as an off-white, homogeneous (TLC, silica, 5:1 hexanes–ethyl acetate) solid: mp 61–62°C; FT-IR ($CHCl_3$ cast) 1619, 1459, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.12 (s, 3 H), 2.22 (s, 3 H), 3.78 (s, 3 H), 3.96 (br s, 2 H), 5.02 (s, 2 H), 7.30–7.45 (m, 3 H), 7.55–7.62 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.61, 14.13, 61.01, 74.99, 102.92, 117.50, 128.03, 128.39, 128.52, 130.02, 137.43, 139.05, 144.31, 147.30; exact mass, *m/z* calcd for $C_{16}H_{18}{}^{81}BrNO_2$ 337.0500, found 337.0504.

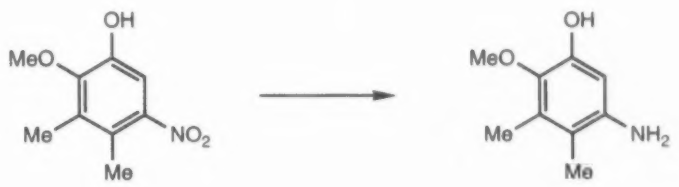
N-[2-Bromo-4-methoxy-5,6-dimethyl-3-(phenylmethoxy)-phenyl]-4-methyl-N-[(4-methylphenyl)sulfonyl]benzene-sulfonamide (107).

106 **107**

p-Toluenesulfonyl chloride (152.3 mg, 0.799 mmol) and pyridine (0.10 mL, 1.24 mmol) were added to a stirred solution of **106** (186.6 mg, 0.555 mmol) in CH_2Cl_2 (25 mL). After 16 h, the reaction was less than 50% complete (TLC, silica, 5:1 hexanes–ethyl acetate). Further portions of *p*-toluenesulfonyl chloride (140 mg, 0.734 mmol) and pyridine (0.15 mL, 1.86 mmol) were added. After an additional 24 h, little **106** remained (TLC). The solution was washed with HCl (1.2 N), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **107** (320.1 mg, 89%) as a white homogeneous (TLC, silica, 5:1 hexanes–ethyl acetate) crystalline solid: mp 248–249°C; FT-IR ($CHCl_3$ cast) 1377, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.86 (s, 3 H), 2.18 (s, 3 H), 2.48 (s, 6 H), 3.91 (s, 3 H), 4.99 (s, 2 H), 7.35–7.50 (m, 7 H), 7.50–7.60 (m, 2 H), 7.95–8.05 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.07, 18.33, 21.76, 60.84, 74.97, 121.52, 128.25, 128.48, 128.63, 129.31, 129.53, 129.94, 131.44, 136.89, 137.02, 138.49, 145.18, 148.12, 153.55; exact mass, *m/z* calcd for $C_{30}H_{30}{}^{81}BrNO_6S_2$ 645.0677, found 645.0679. Anal. Calcd

for $C_{30}H_{30}BrNO_6S_2$: C, 55.90; H, 4.69; N, 2.17; S, 9.95. Found: C, 55.81; H, 5.04; N, 2.30; S, 10.09.

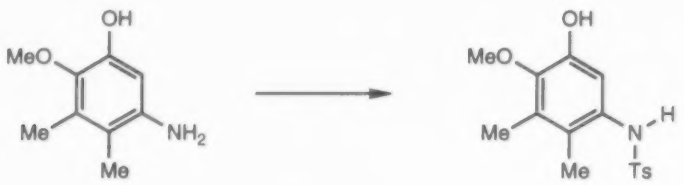
5-Amino-2-methoxy-3,4-dimethylphenol (79).[44b,54]



103 **79**

The preparation of this compound by a different method has been reported,[44b] but without experimental details. Hydrazine hydrate (0.16 mL, 3.3 mmol) was added to a refluxing mixture of **103** (336.8 mg, 1.71 mmol), activated carbon (40 mg, 3.3 mmol), and $FeCl_3 \cdot 6H_2O$ (40 mg, 0.15 mmol) in MeOH (25 mL). After being refluxed overnight, hydrazine hydrate (0.10 mL, 2.1 mmol) was added, and the mixture was refluxed a further 3 h. The mixture was cooled, filtered through silica gel, and evaporated. The residue was partitioned between CH_2Cl_2 and H_2O. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated to give **79** (230.1 mg, 81%) as an off-white, homogeneous (TLC, silica, 2:1 hexanes–ethyl acetate) solid: FT-IR ($CHCl_3$ cast) 2920, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.99 (s, 3 H), 2.20 (s, 3 H), 3.69 (s, 3 H), 2.5–6.0, (br s, 3 H), 6.32 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.63, 12.83, 61.20, 100.31, 113.23, 129.70, 138.50, 141.16, 146.94; exact mass, *m/z* calcd for $C_9H_{13}NO_2$ 167.0946, found 167.0947.

_N_-(5-Hydroxy-4-methoxy-2,3-dimethylphenyl)-4-methylbenzenesulfonamide (108).



79 **108**

p-Toluenesulfonyl chloride (200.3 mg, 1.05 mmol) and pyridine (0.090 mL, 1.1 mmol) were added to a stirred solution of **79** (142.3 mg, 0.852 mmol) in CH_2Cl_2 (25 mL). After being stirred for 16 h, the solution was washed with HCl (1.2 N) and then extracted with aqueous NaOH (2.5 N). The basic extract was acidified with concentrated HCl, and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and evaporated to give **108** (195.3 mg, 71%) as an off-white, homogeneous (TLC, silica, 2:1 hexanes–ethyl acetate) solid: mp 151–152°C; FT-IR ($CHCl_3$ cast) 3430, 3270, 1484, 1324, 1304, 1291, 1160, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.91 (s, 3 H), 2.13 (s, 3 H), 2.41 (s, 3 H), 3.71 (s, 3 H), 5.56 (s, 1 H), 6.33 (s, 1 H), 6.63 (s, 1 H), 7.24 (d, J = 8 Hz, 2 H), 7.63 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.10, 13.74, 21.51, 60.96, 110.70, 124.73, 127.32, 129.60, 130.30, 130.42, 136.80, 143.69, 144.34, 146.67; exact mass, m/z calcd for $C_{16}H_{19}NO_4S$ 321.1035, found 321.1031.

_N_-[2-Bromo-3-hydroxy-4-methoxy-5,6-dimethylphenyl]-4-methylbenzenesulfonamide (109).

108 **109**

Bromine (4 drops) was added to a stirred solution of **108** (108.0 mg, 0.336 mmol) in CH_2Cl_2 (25 mL). After being stirred for 45 min in the dark, the solution was stirred 5 min with Na_2SO_3 (0.7 N, 15 mL). The organic phase was extracted with NaOH (2.5 N). The combined aqueous phases were acidified with concentrated HCl, and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and evaporated to give **109** (131.8 mg, 98%) as an off-white, homogeneous (TLC, silica, 2:1 hexanes–ethyl acetate) solid: mp 151–153°C; FT-IR ($CHCl_3$ cast) 3420, 3270, 1454, 1180, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.22 (s, 3 H), 2.33 (s, 3 H), 2.41 (s, 3 H), 3.78 (s, 3 H), 5.66, (s, 1 H), 6.12 (s, 1 H), 7.23 (d, J = 10 Hz, 2 H), 7.54 (d, J = 10 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.21, 17.18, 21.63, 60.99, 107.75, 127.69, 128.67, 129.53, 130.48, 131.15, 137.14, 143.91, 144.43, 145.25; exact mass, m/z calcd for $C_{16}H_{18}{}^{81}BrNO_4S$ 401.0120, found 401.0120.

4-Methoxy-2,3-dimethyl-1-nitro-5-(phenylmethoxy)-benzene (110).

103 **110**

A mixture of **103** (2.52 g, 12.8 mmol) in CH_2Cl_2 (150 mL), aqueous NaOH (2 N, 150 mL), benzyl bromide (2.50 mL, 21.0 mmol), and tetrabutylammonium bromide (0.49 g, 1.5 mmol) was stirred vigorously for 16 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **110** (3.63 g, 98%) as a white, homogeneous (TLC, silica, 10:1 hexanes–ethyl acetate) solid: mp 64–65°C; FT-IR ($CHCl_3$ cast) 1517, 1344 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.26 (s, 3 H), 2.35 (s, 3 H), 3.86 (s, 3 H), 5.12 (s, 2 H), 7.30–7.48 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.37, 15.08, 60.09, 70.47, 107.30, 125.22, 126.96, 127.77, 128.22, 132.44, 135.58, 145.37, 148.82, 150.71; exact mass, *m/z* calcd for $C_{16}H_{17}NO_4$ 287.1158, found 287.1158. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.75; H, 6.00; N, 5.09.

4-Methoxy-2,3-dimethyl-5-(phenylmethoxy)aniline (111).[54]

110 **111**

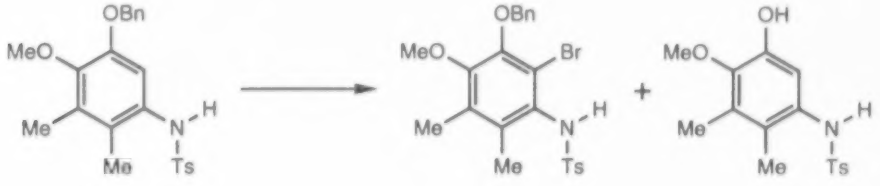
Hydrazine hydrate (523.8 mg, 10.35 mmol) in MeOH (2 mL) was added over 0.5 h to a refluxing mixture of **110** (1.2934 g, 4.50 mmol), activated carbon (111.8 mg, 9.3 mmol), and $FeCl_3 \cdot 6H_2O$ (52.4 mg, 0.194 mmol) in MeOH (40 mL). After being refluxed overnight, the mixture was filtered through Celite and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **110** (726.7 mg) and **111** (490.5 mg, 42%, 96% based on recovered **110**) as an off-white, homogeneous (TLC, silica, 3:1 hexanes–ethyl acetate) solid: mp 75–76°C; FT-IR ($CHCl_3$ cast) 3379, 1622, 1601, 1492, 1488, 1247, 1233, 1083, 1003, 755, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.03 (s, 3 H), 2.21 (s, 3 H), 3.24 (br s, 2 H), 3.76 (s, 3 H), 5.07, (s, 2 H), 6.23 (s, 1 H), 7.25–7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.60, 12.76, 60.66, 70.78, 100.32, 113.94, 127.13, 127.65, 128.46, 131.05, 137.61, 140.37, 140.77, 150.10; exact mass, *m/z* calcd for $C_{16}H_{19}NO_2$ 257.1415, found 257.1415. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.61; H, 7.36; N, 5.30.

N-[4-Methoxy-2,3-dimethyl-5-(phenylmethoxy)phenyl]-4-methylbenzenesulfonamide (112).

111 **112**

p-Toluenesulfonyl chloride (1.51 g, 7.92 mmol) and pyridine (1.00 mL, 12.4 mmol) were added to a stirred solution of **111** (1.69 g, 6.58 mmol) in CH_2Cl_2 (50 mL). After being stirred for 16 h, the solution was washed with HCl (1.2 N) and H_2O, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using first 10:1 hexanes–ethyl acetate, to elute *p*-toluenesulfonyl chloride, and then 1:1 hexanes–ethyl acetate, gave **112** (2.59 g, 96%) as a white homogeneous (TLC, silica, 4:1 hexanes–ethyl acetate) crystalline solid: mp 126–127°C; FT-IR ($CHCl_3$ cast) 3260, 1485, 1331, 1162, 1088 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.82 (s, 3 H), 2.11 (s, 3 H), 2.40 (s, 3 H), 3.77 (s, 3 H), 4.96, (s, 2 H), 6.14 (s, 1 H), 6.73 (s, 1 H), 7.18 (d, J = 9 Hz, 2 H), 7.30–7.45 (m, 5 H), 7.50 (d, J = 9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.79, 13.71, 21.55, 60.44, 70.49, 109.97, 125.33, 127.32, 127.34, 127.87, 128.53, 129.28, 129.49, 131.42, 136.70, 136.96, 143.60, 146.52, 149.54; exact mass, m/z calcd for $C_{23}H_{25}NO_4S$ 411.1504, found 411.1509. Anal. Calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.12; N, 3.40; S, 7.79. Found: C, 67.25; H, 6.01; N, 3.30; S, 8.00.

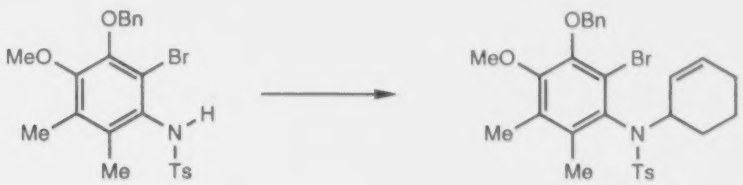
N-[2-Bromo-4-methoxy-5,6-dimethyl-3-(phenylmethoxy)-phenyl]-4-methylbenzenesulfonamide (113).



112 **113** **108**

Bromine (0.37 mL, 7.2 mmol) in CH_2Cl_2 (10 mL) was added to a stirred solution of **112** (2.47 g, 6.01 mmol) in CH_2Cl_2 (40 mL). After being stirred for 10 min in the dark, the solution was stirred 15 min with Na_2SO_3 (0.7 N), acidified with HCl (1.2 N), extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **108** (1.43 g, 60%), identical to that obtained previously (^1H NMR, 200 MHz), and **113** (0.63 g, 21%) as a yellow homogeneous (TLC, silica, 4:1 hexanes–ethyl acetate) crystalline solid: mp 176–177°C; FT-IR ($CHCl_3$ cast) 3260, 1455, 1405, 1332, 1166, 1088 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.23 (s, 3 H), 2.38 (s, 3 H), 2.42 (s, 3 H), 3.83 (s, 3 H), 4.82, (s, 2 H), 6.28 (s, 1 H), 7.18 (d, J = 8 Hz, 2 H), 7.30–7.50 (m, 5 H), 7.52 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.04, 17.79, 21.61, 60.83, 75.12, 116.57, 127.80, 128.33, 128.50, 128.61, 128.84, 129.45, 131.84, 135.55, 136.76, 136.92, 143.88, 147.21, 151.72; exact mass, m/z calcd for $C_{23}H_{24}{}^{79}BrNO_4S$ 489.0609, found 489.0610. Anal. Calcd for $C_{23}H_{24}BrNO_4S$: C, 56.33; H, 4.93; N, 2.86; S, 6.54; O, 13.05; Br, 16.29. Found: C, 56.16; H, 4.97; N, 2.77; S, 6.43; O, 12.90; Br, 16.60.

N-[4-Methoxy-5,6-dimethyl-3-(phenylmethoxy)phenyl]-N-(2-cyclohexenyl)-4-methylbenzenesulfonamide (114).



113 **114**

3-Bromocyclohexene[72] (0.10 mL, 0.86 mmol) was added to a stirred mixture of **113** (61.6 mg, 0.126 mmol) and anhydrous K_2CO_3 (90.6 mg, 0.656 mmol) in anhydrous acetone (25 mL). The mixture was refluxed under argon for 16 h, the acetone was evaporated, and the residue was partitioned between ether and H_2O. The aqueous phase was extracted with ether, and the combined organic phases were washed with H_2O, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **114** (68.3 mg, 95%) as a white solid composed of two isomers (TLC, silica, 10:1 hexanes–ethyl acetate): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40–1.70 (m, 3 H), 1.80–2.05 (m, 3 H), 2.18, 2.21 (two s, 3 H), 2.25 (s, 1.14 H), 2.34 (s, 1.86 H), 2.42 (two s, 3 H), 3.87 (s, 3 H), 4.46 (m, 0.38 H), 4.81 (m, 0.62 H), 4.97 (two s, 2 H), 5.57 (m, 0.38 H), 5.83 (m, 1.62 H), 7.20–7.30 (m, 2 H), 7.30–7.40 (m, 3 H), 7.45–7.55 (m, 2 H), 7.67–7.80 (m, 2 H). Preparative TLC (silica, 10:1 hexanes–ethyl acetate, 18 elutions) gave small samples of each isomer. The more polar had: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43–1.70 (m, 3 H), 1.81–2.05 (m, 3 H), 2.19 (s, 3 H), 2.25 (s, 3 H), 2.42 (s, 3 H), 3.86 (s, 3 H), 4.80 (m, 1 H), 4.96

(s, 2 H), 5.78 (m, 1 H), 5.82 (m, 1 H), 7.25 (d, J = 8 Hz, 2 H), 7.36 (m, 3 H), 7.53 (m, 2 H), 7.76 (d, J = 8 Hz, 2 H), and the less polar had: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40–1.60 (m, 1 H), 1.63–2.12 (m, 5 H), 2.21 (s, 3 H), 2.35 (s, 3 H), 2.42 (s, 3 H), 3.88 (s, 3 H), 4.48 (m, 1 H), 4.97 (s, 2 H), 5.76 (m, 1 H), 5.90 (m, 1 H), 7.24 (d, J = 8 Hz, 2 H), 7.38 (m, 3 H), 7.56 (m, 2 H), 7.72 (d, J = 8 Hz, 2 H). The same material, containing the isomers in a very similar ratio, was fully characterized as described later.

4-Methyl-*N*-[2,3-dimethyl-4-oxo-5-(phenylmethoxy)-2,5-cycloxexadien-1-ylidene)benzenesulfonamide (115).

112 **115**

Concentrated HNO_3 (3 drops) and then concentrated H_2SO_4 (1 drop) were added to a stirred solution of **112** (42.5 mg, 0.103 mmol) in CH_2Cl_2 (5 mL). After being stirred for 1 h, the solution was washed with H_2O (5 mL) and dilute, aqueous $NaHCO_3$ (5 mL), dried ($MgSO_4$), and evaporated to give **115** (39.5 mg, 96%) as a yellow homogeneous (TLC, silica, 4:1 hexanes–ethyl acetate) solid: mp 183.5–185°C; FT-IR (CH_2Cl_2 cast) 559, 696, 781, 1089, 1150, 1247, 1301, 1534, 1599, 1640, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.03, 2.04 (two s, 6 H), 2.45 (s, 3 H), 5.15, (s, 2 H), 7.32–7.50 (m, 8 H), 7.86 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.57,

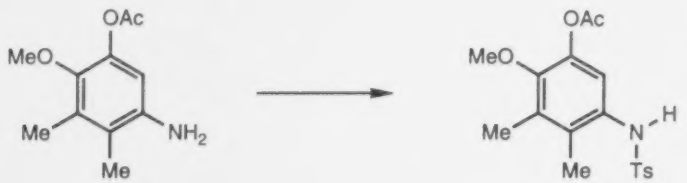
14.07, 21.67, 71.33, 102.92, 103.76, 127.18, 128.18, 128.86, 129.61, 134.09, 138.31, 139.41, 143.60, 143.97, 155.43, 166.09, 180.60; exact mass, *m/z* calcd for $C_{22}H_{21}NO_4S$ 395.1191, found 395.1195.

5-Amino-2-methoxy-3,4-dimethylphenyl acetate (116).

102 **116**

Crude **102** (15.57 g, 0.0651 mol) in ethyl acetate (400 mL) was stirred with 5% Pd/C (6.5 g) under hydrogen for 16 h. The solution was filtered through Celite and evaporated. Flash chromatography of the residue over silica gel, using 4:1 hexanes–ethyl acetate, gave **116** (11.30 g, 74% over two steps) as a brown, homogeneous (TLC, silica, 4:1 hexanes–ethyl acetate) oil: FT-IR ($CHCl_3$ cast) 3370, 1558, 1486, 1243, 1208 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.03 (s, 3 H), 2.20 (s, 3 H), 2.30 (s, 3 H), 3.48 (br s, 2 H), 3.65 (s, 3 H), 6.29 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.83, 13.23, 20.80, 60.99, 107.57, 120.26, 131.54, 140.27, 141.91, 142.62, 169.45; exact mass, *m/z* calcd for $C_{11}H_{15}NO_3$ 209.1052, found 209.1054.

_N_-(5-Acetoxy-4-methoxy-2,3-dimethylphenyl)-4-methylbenzenesulfonamide (117).



116 **117**

p-Toluenesulfonyl chloride (2.51 g, 13.2 mmol) and pyridine (5.0 mL, 62 mmol) were added to a stirred solution of **116** (2.49 g, 11.9 mmol) in CH_2Cl_2 (250 mL). After being stirred overnight, the mixture was washed with aqueous $CuSO_4$ (0.40 M, 2 x 250 mL) and H_2O, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 4:1 hexanes–ethyl acetate, gave **117** (4.11 g, 95%) as an off-white, homogeneous (TLC, silica, 4:1 hexanes–ethyl acetate) solid: mp 139–140°C; FT-IR ($CHCl_3$ cast) 3275, 1768, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.90 (s, 3 H), 2.13 (s, 3 H), 2.29 (s, 3 H), 2.40 (s, 3 H), 3.70 (s, 3 H), 6.56 (s, 1 H), 6.85 (s, 1 H), 7.22 (d, J = 8 Hz, 2 H), 7.40 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.06, 14.24, 20.73, 21.55, 60.84, 118.57, 127.29, 129.61, 129.76, 131.54, 132.07, 136.61, 141.49, 143.73, 148.70, 169.00; exact mass, m/z calcd for $C_{18}H_{21}NO_5S$ 363.1141, found 363.1148.

3-Amino-2-bromo-6-methoxy-4,5-dimethylphenyl acetate (118).

116 **118**

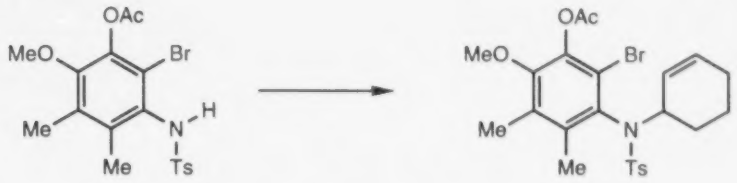
Bromine-dioxane complex[44b] (14.97 g, 60.38 mmol) was added to a stirred solution of **116** (11.30 g, 54.07 mmol) in $CHCl_3$ (150 mL) at 0°C, in the dark. After being stirred for 50 min, the solution was washed with Na_2SO_3 (0.7 N, 3 x 200 mL). The combined aqueous washings were extracted with CH_2Cl_2 (500 mL), and the combined organic phases were dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using 4:1 hexanes–ethyl acetate, gave **118** (13.43 g, 86%) as a brown, homogeneous (TLC, silica, 4:1 hexanes–ethyl acetate) solid: mp 72–73°C; FT-IR ($CHCl_3$ cast) 3370, 1761, 1197, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.11 (s, 3 H), 2.21 (s, 3 H), 2.37 (s, 3 H), 3.68 (s, 3 H), 3.98, (br s, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.77, 14.16, 20.55, 61.13, 101.45, 119.89, 130.15, 139.31, 139.96, 142.86, 168.34; exact mass, *m/z* calcd for $C_{11}H_{14}{}^{79}BrNO_3$ 287.0157, found 287.0155. Anal. Calcd for $C_{11}H_{14}BrNO_3$: C, 45.85; H, 4.90; N, 4.86; O, 16.66. Found: C, 45.66; H, 5.04; N, 4.65; O, 16.93.

N-(3-Acetoxy-2-bromo-4-methoxy-5,6-dimethylphenyl)-4-methylbenzenesulfonamide (119).

118 **119**

p-Toluenesulfonyl chloride (8.28 g, 43.4 mmol) and pyridine (3.40 mL, 42.0 mmol) were added to a stirred solution of **118** (8.00 g, 27.8 mmol) in CH_2Cl_2 (75 mL). After 4 days little of the starting amine remained (TLC, silica, 4:1 hexanes–ethyl acetate). The mixture was washed with HCl (1.2 N), dried ($MgSO_4$) and evaporated to give **119** (10.62 g, 86%) as an off-white, homogeneous (TLC, silica, 4:1 hexanes–ethyl acetate) solid: mp 168–169°C; FT-IR ($CHCl_3$ cast) 3370, 1775, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.21 (s, 3 H), 2.28 (s, 3 H), 2.38 (s, 3 H), 2.40 (s, 3 H), 3.62 (s, 3 H), 6.45 (s, 1 H), 7.21 (d, J = 8 Hz, 2 H), 7.54 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.06, 17.61, 20.28, 21.40, 60.87, 115.73, 127.39, 128.96, 129.40, 131.66, 136.88, 137.91, 139.92, 143.66, 150.28, 167.58; exact mass, m/z calcd for $C_{18}H_{20}{}^{79}BrNO_5S$ 441.0246, found 441.0241. Anal. Calcd for $C_{18}H_{20}BrNO_5S$: C, 48.88; H, 4.56; N, 3.17; O, 18.09; S, 7.25. Found: C, 48.83; H, 4.72; N, 3.31; O, 18.13; S, 7.04.

N-(3-Acetoxy-2-bromo-4-methoxy-5,6-dimethylphenyl)-N-(2-cyclohexenyl)-4-methylbenzenesulfonamide (120).



119 **120**

3-Bromocyclohexene[72] (1.00 mL, 8.63 mmol) was added to a stirred mixture of **119** (2.2456 g, 5.08 mmol) and anhydrous K_2CO_3 (3.04 g, 22.0 mmol) in anhydrous acetone (25 mL). The mixture was refluxed under argon for 16 h, and the acetone was evaporated. The residue was partitioned between CH_2Cl_2 and H_2O and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 4:1 hexanes–ethyl acetate, gave **120** (2.5584 g, 96%) as a white solid composed of two isomers (TLC, silica, 4:1 hexanes–ethyl acetate): mp 48–49°C; FT-IR ($CHCl_3$ cast) 1778, 1191, 1158 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.40–2.13 (m, 6 H), 2.19, 2.21 (two s, 3 H), 2.25 (s, 1.2 H), 2.33, 2.36 (two s, 4.8 H), 2.43 (s, 3 H), 3.76 (s, 3 H), 4.44, (m, 0.62 H), 4.86 (m, 0.38 H), 5.60 (m, 0.38 H), 5.82 (m, 1.62 H), 7.24 (m, 2 H), 7.72 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.38, 19.02, 19.20, 20.60, 21.54, 21.64, 24.41, 24.47, 28.34, 28.89, 59.19, 60.97, 61.15, 119.02, 127.61, 128.17, 128.40, 129.10, 129.23, 129.48, 130.45, 131.14, 131.38, 133.45, 134.58, 139.59, 139.98, 140.57, 140.64, 140.69, 140.77, 143.02, 143.15, 150.74, 150.86, 167.80, 167.87;

exact mass, *m/z* calcd for $C_{24}H_{28}{}^{79}BrNO_5S$ 521.0872, found 521.0871. Anal. Calcd for $C_{24}H_{28}BrNO_5S$: C, 55.18; H, 5.40; N, 2.68; O, 15.31; S, 6.14. Found: C, 55.37; H, 5.55; N, 2.71; O, 15.12; S, 6.37.

5-Acetoxy-1,2,3,4,4a,9a-hexahydro-6-methoxy-7,8-dimethyl-9-[(4-methylphenyl)sulfonyl]carbazole (122).

120 **122**

Method A: Triphenyltin hydride (0.05 mL, 0.20 mmol) in anhydrous benzene (5 mL) and AIBN (2.3 mg, 0.014 mmol) in benzene (5 mL) were added over 10 h (double syringe pump) to a refluxing solution of **120** (87.1 mg, 0.167 mmol) in the same solvent (20 mL). The solution was refluxed a further 6 h, cooled, and evaporated. The residue was taken up in ether, and then stirred for several hours with a saturated aqueous solution of KF. The aqueous phase was extracted with ether, and the combined organic phases were washed with H_2O, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave an inseparable mixture of compounds containing **122** (35–40% yield, calculated by ^1H NMR, 200 MHz) and unreacted **120** (15%). The fragmentation product **117** (10.6 mg, 17%) was also isolated.

Method C: A solution of triphenyltin hydride (0.015 mL, 0.059 mmol), AIBN (1 mg, 0.006 mmol) and **120** (18.1 mg, 0.035 mmol) in anhydrous toluene (2.5 mL) was stirred under argon at 0°C. The solution was irradiated with a sun lamp (CGE model RSM, 275 Watt, 110–125 V) for 2.5 h, and then evaporated. Flash chromatography of the residue over silica gel, using 4:1 hexanes–ethyl acetate, gave 13.0 mg (85%) of a mixture containing **120** and the product of direct reduction **125** in a 2:3 ratio (^{1}H NMR, 200 MHz).

In another experiment, a solution of **120** (115.2 mg, 0.221 mmol) in anhydrous toluene (10 mL) was stirred under argon in a water-cooled vessel. Triphenyltin hydride (0.08 mL, 0.31 mmol) in toluene (5 mL) and AIBN (4.7 mg, 0.029 mmol) in toluene (5 mL) were added over 16 h (double syringe pump) to the solution as it was irradiated with a sun lamp (CGE model RSM, 275 Watt, 110–125 V). The solution was irradiated a further 6 h, and then evaporated. Flash chromatography of the residue over silica gel, using 4:1 hexanes–ethyl acetate, gave 96.3 mg of an inseparable mixture of compounds containing **122** (46% yield, calculated by ^{1}H NMR, 200 MHz), recovered **120** (16%) and **125** (33%).

In a similar experiment, a solution of **120** (273.0 mg, 0.523 mmol) in anhydrous toluene (10 mL) was stirred under argon in a water-cooled vessel. Triphenyltin hydride (0.16 mL, 0.63 mmol) in toluene (5 mL) and AIBN (21 mg, 0.13 mmol) in toluene (5 mL) were added over 18 h (double syringe pump) to the solution as it was irradiated with a sun lamp (CGE model RSM, 275 Watt, 110–125 V). The solution was evaporated, dissolved in ethanolic KOH (5%

w/v, 10 mL), and stirred for 1 h. The resulting solution was evaporated, and the residue was dissolved in H_2O, acidified with HCl (1.2 N), and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave the hydrolyzed cyclization product **123** (43.0 mg, 21%), hydrolyzed starting material **121** (95 mg, 38%), and the hydrolyzed product of direct reduction **126** (52 mg, 25%).

Method D: Samarium iodide (1.0 M in THF, 5.0 mL, 0.50 mmol) and dry HMPA (0.7 mL) were added to **120** (73.9 mg, 0.142 mmol), and the mixture was stirred overnight under argon at room temperature. The solution was diluted with ether, washed with HCl (1.2 N) and with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave a complicated mixture, of which the major component was unreacted starting material (^1H NMR, 200 MHz). A small amount of the product of direct reduction, **125**, and only a trace of cyclized material **122** were identified (^1H NMR, 200 MHz).

N-(2-Bromo-3-hydroxy-4-methoxy-5,6-dimethylphenyl)-N-(2-cyclohexenyl)-4-methylbenzenesulfonamide (121).

120 **121**

A solution of **120** (2.8362 g, 5.43 mmol) in ethanolic KOH (3.5% w/v, 50 mL) was stirred for 1 h, diluted with H_2O (100 mL), acidified with HCl (1.2 N), and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and evaporated to afford **121** (2.58 g, 98%) as a white solid composed of two isomers (TLC, silica, 4:1 hexanes–ethyl acetate): mp 168.5–169.5°C; FT-IR ($CHCl_3$ cast) 3430, 1482, 1156, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.40–2.10 (m, 6 H), 2.13, 2.17, 2.19, 2.24 (four s, 6 H), 2.43 (s, 3 H), 3.81 (s, 3 H), 4.51 (m, 0.62 H), 4.79 (m, 0.38 H), 5.55–5.92 (m, 3 H), 7.25 (m, 2 H), 7.74 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.31, 18.45, 18.55, 21.55, 21.60, 21.68, 24.39, 24.48, 28.23, 28.74, 59.11, 60.57, 60.74, 60.81, 111.44, 112.50, 127.70, 128.23, 128.37, 129.09, 129.22, 129.48, 129.99, 130.07, 130.35, 132.62, 133.71, 133.90, 139.57, 139.96, 143.02, 143.14, 144.79, 144.85, 145.54, 145.63; exact mass, *m/z* calcd for $C_{22}H_{26}{}^{79}BrNO_4S$ 479.0766, found 479.0766. Anal. Calcd for $C_{22}H_{26}BrNO_4S$: C, 55.00; H, 5.46; N, 2.92; S, 6.67; Br, 16.63. Found: C, 55.09; H, 5.55; N, 3.20; S, 6.70; Br 16.78.

1,2,3,4,4a,9a-Hexahydro-5-hydroxy-6-methoxy-7,8-dimethyl-9-[(4-methylphenyl)sulfonyl]carbazole (123).

121 **123**

Method A: Triphenyltin hydride (0.04 mL, 0.16 mmol) in anhydrous benzene (5 mL) and AIBN (2.8 mg, 0.017 mmol) in benzene (5 mL) were added over 10 h (double syringe pump) to a refluxing solution of **121** (45.6 mg, 0.095 mmol) in the same solvent (20 mL). The solution was refluxed a further 8 h, cooled, and evaporated. The residue was taken up in ether, and then stirred for several hours with a saturated aqueous solution of KF. The aqueous phase was extracted with ether, and the combined organic phases were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 4:1 hexanes–ethyl acetate, gave unreacted **121** (29.7 mg, 65%), the fragmentation product **108** (0.8 mg, 3%), and **123** (5.6 mg, 15%, 42% based on recovered **121**) as a white, homogeneous (TLC, silica, 4:1 hexanes–ethyl acetate) solid: mp 184–185°C; FT-IR ($CHCl_3$ cast) 3450, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.80–1.62 (m, 6 H), 1.95 (m, 1 H), 2.22 (s, 3 H), 2.33 (s, 3 H), 2.40 (s, 3 H), 2.50 (m, 1 H), 2.66 (m, 1 H), 3.76 (s, 3 H), 4.18 (dt, J = 10, 6 Hz, 1 H), 5.48 (s, 1 H), 7.17 (d, J = 8 Hz, 2 H), 7.46 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.00, 16.99, 21.10, 21.63, 23.44, 24.52, 28.58, 39.84, 61.08,

64.93, 121.39, 124.36, 127.44, 128.87, 129.42, 136.38, 138.17, 143.60, 143.69, 144.38; exact mass, *m/z* calcd for $C_{22}H_{27}NO_4S$ 401.1660, found 401.1658. Anal. Calcd for $C_{22}H_{27}NO_4S$: C, 65.81; H, 6.78; N, 3.49; S, 7.98. Found: C, 65.43; H, 7.07; N, 3.29; S, 7.87.

Method B: Triphenyltin hydride (0.07 mL, 0.26 mmol) and triethylborane (1.0 M in THF, 0.14 mL, 0.214 mmol) were added to a stirred solution of **121** (64.8 mg, 0.135 mmol) in hexanes (10 mL, distilled from CaH_2 in the presence of O_2). Air (18 mL, 1.15 mmol O_2) was injected into the solution over 18 h (syringe pump). The solution was extracted with CH_3CN, and the CH_3CN phase was evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave unreacted **121** (36.4 mg, 56%) and **123** (9.6 mg, 18%, 40% based on recovered **121**) as a white, homogeneous (TLC, silica, 4:1 hexanes–ethyl acetate) solid, identical to that prepared previously (^1H NMR, 200 MHz).

***N*-[2-Bromo-4-methoxy-5,6-dimethyl-3-(phenylmethoxy)-phenyl]-*N*-(2-cyclohexenyl)-4-methylbenzenesulfonamide (114).**

121 **114**

A mixture of **121** (1.5408 g, 3.21 mmol) in CH_2Cl_2 (30 mL), aqueous NaOH (1.25 N, 30 mL), benzyl bromide (1.20 mL, 10.1

mmol), and tetrabutylammonium bromide (0.12 g, 0.37 mmol) was stirred vigorously for 16 h. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **114** (1.7285 g, 94%) as a white solid composed of two isomers (TLC, silica, 10:1 hexanes–ethyl acetate): mp 143–144°C; FT-IR ($CHCl_3$ cast) 1459, 1398, 1343, 1157, 1092, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.40–1.70 (m, 3 H), 1.80–2.05 (m, 3 H), 2.18, 2.21 (two s, 3 H), 2.25 (s, 1.14 H), 2.34 (s, 1.86 H), 2.42 (two s, 3 H), 3.87 (s, 3 H), 4.46 (m, 0.38 H), 4.81 (m, 0.62 H), 4.97 (two s, 2 H), 5.57 (m, 0.38 H), 5.83 (m, 1.62 H), 7.20–7.30 (m, 2 H), 7.30–7.40 (m, 3 H), 7.45–7.55 (m, 2 H), 7.67–7.80 (m, 2 H); Variable Temperature ^1H NMR (C_7D_7, 400 MHz) 0°C: δ 1.20–1.74 (m, 4 H), 1.83–1.89 (m, 0.60 H), 1.94 (two s, 3 H), 2.00, 2.05 (two s, 3 H), 1.96–2.16 (m, 1.40 H), 2.36 (s, 1.20 H), 2.48 (s, 1.80 H), 3.48, 3.50 (two s, 3 H), 4.57 (m, 0.60 H), 4.89, 4.91 (two s, 2 H), 5.08 (m, 0.40 H), 5.50 (m, 0.40 H), 5.72 (m, 0.60 H), 6.17 (m, 0.40 H), 6.20 (m, 0.60 H), 6.77 (d, J = 4 Hz, 2 H), 7.06–7.20 (m, 3 H), 7.43 (t, J = 4 Hz, 2 H), 7.84 (t, J = 4 Hz, 2 H); 20°C: δ 1.20–1.74 (m, 4 H), 1.82–1.89 (m, 0.60 H), 1.94 (two s, 3 H), 2.04, 2.06 (two s, 3 H), 1.97–2.11 (m, 1.40 H), 2.35 (s, 1.20 H), 2.48 (s, 1.80 H), 3.51, 3.52 (two s, 3 H), 4.59 (m, 0.60 H), 4.90, 4.92 (two s, 2 H), 5.05 (m, 0.40 H), 5.49 (m, 0.40 H), 5.70 (m, 0.60 H), 6.12 (m, 0.40 H), 6.18 (m, 0.60 H), 6.79 (d, J = 4 Hz, 2 H), 7.05–7.19 (m, 3 H), 7.45 (m, 2 H), 7.84 (t, J = 4 Hz, 2 H); 40°C: δ 1.22–1.75 (m, 4 H), 1.80–1.92 (m,

0.61 H), 1.99 (two s, 3 H), 2.06, 2.08 (two s, 3 H), 2.00–2.13 (m, 1.39 H), 2.36 (s, 1.17 H), 2.49 (s, 1.83 H), 3.51, 3.54 (two s, 3 H), 4.62 (m, 0.61 H), 4.92, 4.94 (two s, 2 H), 5.03 (m, 0.39 H), 5.49 (m, 0.39 H), 5.69 (m, 0.61 H), 6.11 (m, 0.39 H), 6.18 (m, 0.61 H), 6.82 (d, J = 4 Hz, 2 H), 7.06–7.20 (m, 3 H), 7.43 (t, J = 4 Hz, 2 H), 7.84 (t, J = 4 Hz, 2 H); 60°C: δ 1.27–1.76 (m, 4 H), 1.80–1.92 (m, 0.61 H), 1.96 (s, 3 H), 2.03, 2.04 (two s, 3 H), 2.00–2.11 (m, 1.39 H), 2.36 (s, 1.17 H), 2.47 (s, 1.83 H), 3.56, 3.57 (two s, 3 H), 4.64 (m, 0.61 H), 4.93 (s, 2 H), 5.00 (m, 0.39 H), 5.49 (m, 0.39 H), 5.67 (m, 0.61 H), 6.10 (m, 0.39 H), 6.16 (m, 0.61 H), 6.84 (d, J = 4 Hz, 2 H), 7.07–7.20 (m, 3 H), 7.44 (m, 2 H), 7.82 (t, J = 4 Hz, 2 H); 80°C: δ 1.27–1.77 (m, 4 H), 1.80–1.90 (m, 0.60 H), 2.00 (s, 3 H), 2.06, 2.08 (two s, 3 H), 2.03–2.13 (m, 1.40 H), 2.34 (s, 1.20 H), 2.44 (s, 1.80 H), 3.54, 3.55 (two s, 3 H), 4.64 (m, 0.60 H), 4.93 (s, 2 H), 4.96 (m, 0.40 H), 5.50 (m, 0.40 H), 5.66 (m, 0.60 H), 6.07 (m, 0.40 H), 6.14 (m, 0.60 H), 6.86 (d, J = 4 Hz, 2 H), 7.06–7.19 (m, 3 H), 7.42 (t, J = 4 Hz, 2 H), 7.81 (t, J = 4 Hz, 2 H); 100°C: δ 1.22–1.77 (m, 4 H), 1.79- 1.92 (m, 0.60 H), 2.04 (s, 3 H), 2.08, 2.10 (two s, 3 H), 1.97–2.13 (m, 1.40 H), 2.33 (s, 1.20 H), 2.43 (s, 1.80 H), 3.60 (two s, 3 H), 4.66 (m, 0.60 H), 4.93 (s, 2 H), 4.90–4.98 (m, 0.40 H), 5.50 (m, 0.40 H), 5.66 (m, 0.60 H), 6.07 (m, 0.40 H), 6.14 (m, 0.60 H), 6.88 (d, J = 4 Hz, 2 H), 7.07–7.20 (m, 3 H), 7.42 (t, J = 4 Hz, 2 H), 7.80 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.13, 18.93, 19.01, 21.51, 21.60, 21.66, 24.40, 24.48, 28.28, 28.74, 58.89, 60.71, 74.75, 74.86, 120.23, 121.25, 127.82, 128.11, 128.16, 128.36, 128.45, 128.61, 128.64, 128.98, 129.11, 129.24, 130.24, 130.87, 131.10, 134.16,

136.93, 136.97, 138.36, 138.45, 139.56, 139.96, 142.91, 143.04, 147.57, 152.08, 152.18; exact mass, *m/z* calcd for $C_{29}H_{32}{}^{81}BrNO_4S$ 571.1215, found 571.1205. Anal. Calcd for $C_{29}H_{32}BrNO_4S$: C, 61.05; H, 5.65; N, 2.46; O, 11.22; S, 5.62. Found: C, 60.90; H, 5.85; N, 2.44; O, 10.91; S, 5.53.

1,2,3,4,4a,9a-Hexahydro-6-methoxy-7,8-dimethyl-9-[(4-methylphenyl)sulfonyl]-5-(phenylmethoxy)carbazole (124).

114 **124**

Method A: Triphenyltin hydride (0.70 mL, 2.74 mmol) in anhydrous benzene (5 mL) and AIBN (157.3 mg, 0.960 mmol) in benzene (5 mL) were added over 10 h (double syringe pump) to a refluxing solution of **114** (985.9 mg, 1.730 mmol) in the same solvent (40 mL). The solution was refluxed a further 6 h, cooled, and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **124** (333.2 mg, 39%) as a white, homogeneous (TLC, silica, 10:1 hexanes–ethyl acetate) solid: mp 186°C; FT-IR ($CHCl_3$ cast) 1452, 1352, 1137 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.94–1.44 (m, 5 H), 1.55 (m, 1 H), 1.99 (m, 1 H), 2.26 (s, 3 H), 2.30–2.50 (m, 1 H), 2.36 (s, 3 H), 2.40 (s, 3 H), 2.60 (m, 1 H), 3.82 (s, 3 H), 4.18 (dt, J = 10, 6 Hz, 1 H), 4.73 (s, 2 H), 7.15 (d, J = 8 Hz, 2 H), 7.34 (s, 5 H), 7.43 (d, J = 8 Hz, 2 H); ^{13}C NMR

($CDCl_3$, 75.5 MHz) δ 12.69, 17.38, 21.21, 21.54, 23.31, 24.54, 28.63, 40.01, 60.66, 64.64, 74.80, 127.49, 128.04, 128.09, 128.49, 128.68, 128.78, 129.34, 130.92, 136.10, 137.32, 137.68, 143.66, 147.17, 150.19; exact mass, *m/z* calcd for $C_{29}H_{33}NO_4S$ 491.2130, found 491.2135. Anal. Calcd for $C_{29}H_{33}NO_4S$: C, 70.85; H, 6.77; N, 2.85; S, 6.52. Found: C, 71.12; H, 6.76; N, 2.83; S, 6.30.

Method B: Triphenyltin hydride (0.27 mL, 1.1 mmol) in anhydrous benzene (10 mL) and air (32 mL, 0.26 mmol O_2) were added over 20 h (double syringe pump) to a stirred solution of triethylborane (1.0 M in hexanes, 1.10 mL, 1.1 mmol) and **114** (546.9 mg, 0.959 mmol) in benzene (40 mL). After 20 h, the reaction was still incomplete (TLC, silica, 10:1 hexanes–ethyl acetate). Triethylborane (1.0 M in hexanes, 1.00 mL, 1.0 mmol) was added, and then triphenyltin hydride (0.15 mL, 0.59 mmol) in benzene (10 mL) and air (38 mL, 0.31 mmol O_2) were added over 24 h. The solution was evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **124** (173.2 mg, 37%) as a white, homogeneous (TLC, silica, 10:1 hexanes–ethyl acetate) solid, identical to that prepared previously (^1H NMR, 200 MHz).

Method C: A solution of **114** (94.3 mg, 0.165 mmol) in anhydrous toluene (15 mL) was stirred under argon in a water-cooled vessel. Triphenyltin hydride (0.055 mL, 0.22 mmol) in toluene (5 mL) and AIBN (10.1 mg, 0.062 mmol) in toluene (5 mL) were added over 15 h (double syringe pump) to the solution as it was irradiated with a sun lamp (CGE model RSM, 275 Watt, 110–125

V). Evaporation of the solution, and flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave 56 mg of a mixture containing **124** (23% yield, calculated by ^{1}H NMR, 200 MHz), unreacted **114** (16%) and the product of direct reduction **127** (28%).

Carbazomycin B (2).

124 **2**

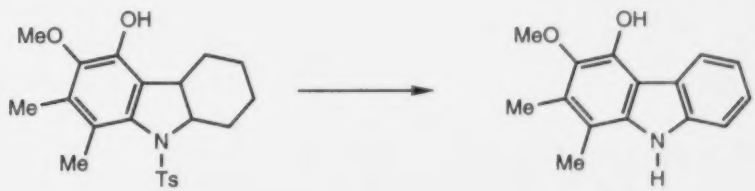
A mixture of **124** (46.2 mg, 0.0941 mmol), maleic acid (37.1 mg, 0.320 mmol) and 5% Pd/C (26.0 mg) in triglyme (4 mL) was refluxed under argon for 3 days. The mixture was filtered through Celite, diluted with ether, washed with H_2O, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **2**[1] (10.0 mg, 44%), identical to that prepared as described later (^{1}H NMR, 200 MHz).

1,2,3,4,4a,9a-Hexahydro-5-hydroxy-6-methoxy-7,8-dimethyl-9-[(4-methylphenyl)sulfonyl]carbazole (123).

124 **123**

Compound **124** (120.2 mg, 0.245 mmol) in ethyl acetate (10 mL) was shaken with 5% Pd/C (62 mg) under hydrogen at 65 psi in a Parr shaker for 18 h. The solution was filtered through Celite and evaporated. Flash chromatography of the residue over silica gel, using 6:1 hexanes–ethyl acetate, gave **123** (69.6 mg, 70%), identical to that prepared previously (^{1}H NMR, 200 MHz).

Carbazomycin B (2).



123 **2**

A mixture of **123** (25.2 mg, 0.0628 mmol), maleic acid (30.9 mg, 0.266 mmol) and 5% Pd/C (11.5 mg) in triglyme (5 mL) was heated to reflux (240°C bath temperature) for 40 h. The mixture was diluted with CH_2Cl_2, washed with H_2O, dried ($MgSO_4$) and evaporated. The residue was dried in vacuo at 60°C for 3 h. Flash chromatography of the residue over silica gel, using 10:1

hexanes–ethyl acetate, gave **2**[1] (8.7 mg, 60%), identical to that prepared as described later (^{1}H NMR, 200 MHz).

1,2,3,4,4a,9a-Hexahydro-5-hydroxy-6-methoxy-7,8-dimethylcarbazole (132).

124 **132**

Sodium naphthalenide (0.50 M in THF, 2.5 mL, 1.25 mmol) was added to a stirred solution of **124** (78.3 mg, 0.159 mmol) in THF (8 mL). After being stirred for 2 min, the solution was quenched with saturated aqueous NH_4Cl (5 drops), diluted with H_2O, neutralized with HCl (1.2 N), and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using first hexanes (to elute naphthalene) and then 1:1 hexanes–ethyl acetate, gave **132** (25.5 mg, 65%) as an unstable, clear, homogeneous (TLC, silica, 10:1 hexanes–ethyl acetate) oil: FT-IR ($CHCl_3$ cast) 3370, 2930, 1460, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.36–1.96 (m, 8 H), 1.97 (s, 3 H), 2.15 (s, 3 H), 3.09–3.24 (m, 1 H), 3.69 (s, 3 H), 3.72–3.78 (m, 1 H), 4.76 (broad s, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.43, 13.12, 21.29, 23.12, 27.14, 28.90, 39.55, 59.36, 61.19, 110.04, 117.06, 127.23, 139.02, 143.11, 146.34; exact mass, *m/z* calcd for $C_{15}H_{21}NO_2$ 247.1573, found 247.1574.

Carbazomycin B (2).

132 **2**

A slow stream of dry argon was bubbled for 56 h through a hot (260°C) mixture of **132** (25.5 mg, 0.1032 mmol) and 10% Pd/C (17.7 mg) in triglyme (7 mL). The mixture was cooled, filtered through silica gel, and evaporated at reduced pressure using a Kugelrohr distillation apparatus. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **2**[1] (17.8 mg, 71%) as an off-white, homogeneous (TLC, silica, 10:1 hexanes–ethyl acetate) solid: mp 148°C [lit.[1a] mp 158.5–160°C (*n*-hexane–ethyl acetate)]; FT-IR ($CHCl_3$ cast) 3425, 1454, 1411 cm^{-1}; ^1H NMR[1b] ($CDCl_3$, 200 MHz) δ 2.34 (s, 3 H), 2.38 (s, 3 H), 3.81 (s, 3 H), 6.09 (s, 1 H), 7.17–7.25 (m, 1 H), 7.33–7.40 (m, 2 H), 7.76 (s, 1 H), 8.25 (d, J = 7.5 Hz, 1 H); ^{13}C NMR[1b] ($CDCl_3$, 75.5 MHz) δ 12.77, 13.18, 61.49, 109.30, 109.36, 109.99, 119.47, 122.65, 123.27, 124.74, 126.98, 136.76, 138.46, 139.26, 142.02; exact mass, *m/z* calcd for $C_{15}H_{15}NO_2$ 241.1102, found 241.1101. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.91; H, 6.27; N, 5.98.

1-Deutero-3-(phenylsulfonyl)cyclohex-2-enol (137).

133 **137**

Compound **133** was converted by the literature procedure[56] into **137**, using $NaBD_4$ instead of $NaBH_4$ in the reduction step. Compound **137** was obtained as a clear, homogeneous (TLC, silica, 2:1 hexanes–ethyl acetate) oil in 75% overall yield from **133** and had: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.47–1.60 (m, 2 H), 1.75–1.91 (m, 2 H), 2.15 (m, 2 H), 3.50 (m, 1 H), 7.00 (s, 1 H), 7.48–7.66 (m, 3 H), 7.86 (m, 2 H). A small signal at δ 4.3 indicated the presence of *ca* 7% nondeutero alcohol (H instead of D). The material was used directly in the next step without full characterization.

3-Bromo-1-(phenylsulfonyl)cyclohexene (138).

136 **138**

Carbon tetrabromide (787.1 mg, 2.37 mmol) and triphenylphosphine (615.4 mg, 2.35 mmol) were added to a stirred solution of **136**[56] (471.9 mg, 1.98 mmol) in CH_2Cl_2 (10 mL). Stirring was continued overnight, and the mixture was then evaporated. Flash chromatography of the residue over silica gel, using 3:1 hexanes–ether, gave **138** (465.8 mg, 78%) as a clear, homogeneous (TLC,

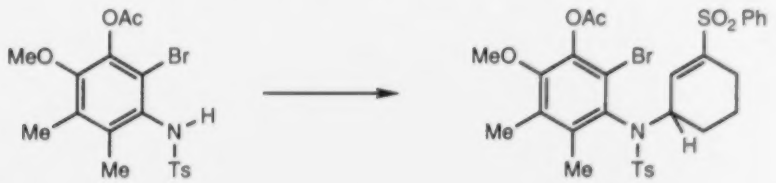
silica, 2:1 hexanes–ethyl acetate) oil: FT-IR ($CHCl_3$ cast) 1446, 1306, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.67–2.22 (m, 4 H), 2.33 (m, 2 H), 4.86 (m, 1 H), 7.12 (m, 1 H), 7.50–7.70 (m, 3 H), 7.86 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.23, 22.63, 31.07, 43.75, 128.15, 129.29, 133.64, 136.05, 138.44, 141.99; exact mass, *m/z* calcd for $C_{12}H_{13}{}^{81}BrSO_2$ 301.9799, found 301.9809.

3-Bromo-3-deutero-1-(phenylsulfonyl)cyclohexene (139).

137 **139**

Carbon tetrabromide (1.52 g, 4.58 mmol) and triphenylphosphine (1.18 g, 4.50 mmol) were added to a stirred solution of **137** (914.0 mg, 3.82 mmol) in CH_2Cl_2 (10 mL). The solution was stirred overnight, and then evaporated. Flash chromatography of the residue over silica gel, using 3:1 hexanes–ether, gave **139** (773.2 mg, 67%) as a clear, homogeneous (TLC, silica, 2:1 hexanes–ethyl acetate) oil containing (^1H NMR, 200 MHz) *ca.* 7% of the corresponding protium species: FT-IR ($CHCl_3$ cast) 1446, 1305, 1151 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.67–2.20 (m, 4 H), 2.32 (m, 2 H), 7.10 (s, 1 H), 7.52–7.72 (m, 3 H), 7.88 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.25, 22.70, 30.98, 128.22, 129.33, 133.66, 136.00, 138.52, 142.11; exact mass, *m/z* calcd for $C_{12}H_{12}{}^{81}BrO_2SD$ 302.9862, found 302.9870.

N-(3-Acetoxy-2-bromo-4-methoxy-5,6-dimethylphenyl)-N-[3-(phenylsulfonyl)-2-cyclohexenyl]-4-methylbenzenesulfonamide (140).



119 **140**

A mixture of **119** (550.1 mg, 1.24 mmol), the allylic bromide **138** (451.1 mg, 1.50 mmol), and anhydrous K_2CO_3 (0.99 g, 7.2 mmol) in anhydrous acetone (15 mL) was refluxed under argon for 18 h. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and H_2O. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 100:1 CH_2Cl_2–ether, gave **140** (800.0 mg, 97%) as a white solid composed of two isomers (TLC, silica, 2:1 hexanes–ethyl acetate). The material was subjected four times to flash chromatography over silica gel, using 100:1 CH_2Cl_2–ether, in order to effect partial separation of the isomers. The less polar isomer was obtained pure (^1H NMR, 400 MHz) and had: mp 208–208.5°C (after crystallization from CH_2Cl_2–petroleum ether); FT-IR ($CHCl_3$ cast) 1774, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49 (m, 1 H), 1.88 (m, 1 H), 1.98–2.15 (m, 3 H), 2.20 (s, 3 H), 2.25 (m, 1 H), 2.34 (s, 3 H), 2.37 (s, 3 H), 2.43 (s, 3 H), 3.78 (s, 3 H), 4.39 (m, 1 H), 7.32 (d, J = 8 Hz, 2 H), 7.46 (s, 1 H), 7.58 (t, J = 8 Hz, 2 H), 7.62 (d, J = 8

Hz, 1 H), 7.68 (d, J = 8 Hz, 2 H), 7.92 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.39, 19.21, 20.56, 21.42, 21.58, 22.53, 28.83, 61.02, 61.92, 118.42, 127.95, 129.25, 129.72, 129.88, 131.93, 133.42, 133.90, 137.55, 138.84, 138.87, 140.63, 140.84, 140.89, 143.65, 151.09, 167.83; exact mass, m/z calcd for $C_{30}H_{32}{}^{81}BrNO_7S_2$ 663.0783, found 663.0784. The more polar isomer was also obtained pure (^1H NMR, 300 MHz) and had: mp 189–191°C (after crystallization from CH_2Cl_2–petroleum ether); FT-IR ($CHCl_3$ cast) 1774, 1151 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (m, 1 H), 1.56 (m, 1 H), 1.83 (m, 3 H), 2.19 (s, 3 H), 2.22 (m, 1 H), 2.28 (s, 3 H), 2.33 (s, 3 H), 2.47 (s, 3 H), 3.77 (s, 3 H), 4.98 (m, 1 H), 7.31 (m, 3 H), 7.48 (m, 2 H), 7.58 (m, 1 H), 7.76 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.39, 19.13, 20.59, 21.36, 21.65, 22.32, 26.60, 58.37, 61.02, 119.52, 128.11, 129.13, 129.70, 131.60, 132.12, 133.30, 138.40, 138.76, 138.93, 140.42, 140.71, 141.03, 143.86, 151.30, 167.67; exact mass, m/z calcd for $C_{30}H_{32}{}^{81}BrNO_7S_2$ 663.0783, found 663.0779. Analysis was performed on the isomer mixture. Anal. Calcd for $C_{30}H_{32}BrNO_7S_2$: C, 54.38; H, 4.87; N, 2.11; O, 16.90; S, 9.68. Found: C, 54.25; H, 4.89; N, 1.95; O, 16.83; S, 9.74.

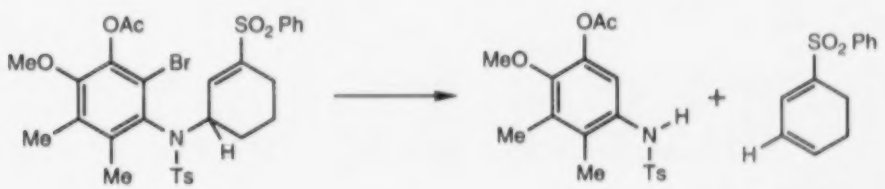
N-(3-Acetoxy-2-bromo-4-methoxy-5,6-dimethylphenyl)-N-[1-deutero-3-(phenylsulfonyl)-2-cyclohexenyl]-4-methylbenzenesulfonamide (141).

119 **141**

A mixture of **119** (202.3 mg, 0.458 mmol), the allylic bromide **139** (238.2 mg, 0.789 mmol), and anhydrous K_2CO_3 (0.71 g, 5.1 mmol) in acetone (10 mL) was refluxed under argon for 16 h. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 2:1 hexanes–ethyl acetate, gave **141** (295.8 mg, 97%) as a white solid composed of two isomers (TLC, silica, 2:1 hexanes–ethyl acetate): mp 188–202°C; FT-IR (CH_2Cl_2 cast) 1776, 1151 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.44–1.67 (m, 1 H), 1.67–2.10 (m, 4 H), 2.16, 2.18 (two s, 4 H), 2.25, 2.30, 2.33, 2.36 (four s, 6 H), 2.43, 2.48 (two s, 3 H), 3.75, 3.78 (two s, 3 H), 7.32 (m, 2 H), 7.45–7.76 (m, 7 H), 7.91 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.30, 13.35, 19.04, 19.15, 20.50, 21.24, 21.35, 21.54, 22.26, 22.52, 26.39, 28.63, 57.89, 60.94, 118.48, 119.49, 127.92, 127.94, 128.02, 129.06, 129.21, 129.62, 129.66, 131.52, 131.86, 131.98, 133.25, 133.38, 133.79, 137.43, 138.30, 138.70, 138.85, 140.51, 140.56, 140.63,

140.82, 140.93, 141.08, 143.60, 143.78, 151.10, 151.27, 167.58, 167.74; exact mass, *m/z* calcd for $C_{30}H_{31}{}^{79}BrNO_7S_2D$ 662.0866, found 662.0865. Careful flash chromatography (silica gel, 4:1 hexanes–ethyl acetate) of the isomer mixture gave the less polar isomer **141a** as a white homogeneous (TLC, silica, 2:1 hexanes–ethyl acetate) solid: mp (after crystallization from CH_2Cl_2–petroleum ether) 207.5–208.5; FT-IR ($CHCl_3$ cast) 1776, 1151 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.49 (m, 1 H), 1.69–2.11 (m, 4 H), 2.21 (s, 3 H), 2.25 (m, 1 H), 2.34 (s, 3 H), 2.37 (s, 3 H), 2.43 (s, 3 H), 3.78 (s, 3 H), 7.30 (d, J = 8 Hz, 2 H), 7.44 (s, 1 H), 7.50–7.70 (m, 5 H), 7.92 (d, J = 8 Hz, 2 H); exact mass, *m/z* calcd for $C_{30}H_{31}{}^{81}BrNO_7S_2D$ 664.0846, found 664.0842.

Fragmentation of *N*-(3-Acetoxy-2-bromo-4-methoxy-5,6-dimethylphenyl)-*N*-[3-(phenylsulfonyl)-2-cyclohexenyl]-4-methylbenzenesulfonamide (major isomer, 140a).

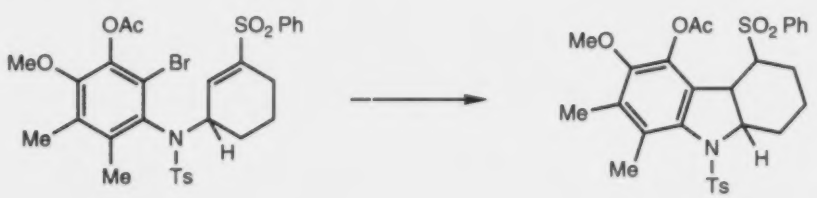


140a **117** **142**

Triphenyltin hydride (0.15 mL, 0.59 mmol) in anhydrous benzene (5 mL) and AIBN (30.5 mg, 0.189 mmol) in benzene (5 mL) were each added over 10 h (double syringe pump) to a refluxing solution of **140a** (252.2 mg, 0.381 mmol) in benzene (50 mL). The mixture was refluxed for a further 10 h, cooled, and

evaporated. Flash chromatography of the residue over silica gel, using 4:1 hexanes–ethyl acetate, to elute **142**, and then 2:1 hexanes–ethyl acetate, to elute **117**, gave **142** (34.4 mg, 41%) as a white, homogeneous (TLC, silica, 2:1 hexanes–ethyl acetate) solid: mp 90–91°C [lit.[57] mp 92–93°C]; FT-IR ($CHCl_3$ cast) 1303, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.31 (m, 4 H), 6.08, 6.11 (two s, 2 H), 7.04 (m, 1 H), 7.47–7.65 (m, 3 H), 7.88 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.13, 22.92, 122.76, 127.89, 129.18, 131.76, 133.22, 133.33, 136.34, 139.78; exact mass, *m/z* calcd for $C_{12}H_{12}O_2S$ 220.0558, found 220.0549. Compound **117** (55.6 mg, 40%) was obtained as a white, homogeneous (TLC, silica, 2:1 hexanes–ethyl acetate) solid, identical (^1H NMR, 200 MHz) to that prepared previously.

5-Acetoxy-1,2,3,4,4a,9a-hexahydro-6-methoxy-7,8-dimethyl-9-[(4-methylphenyl)sulfonyl]-4-(phenylsulfonyl)-carbazole (144).

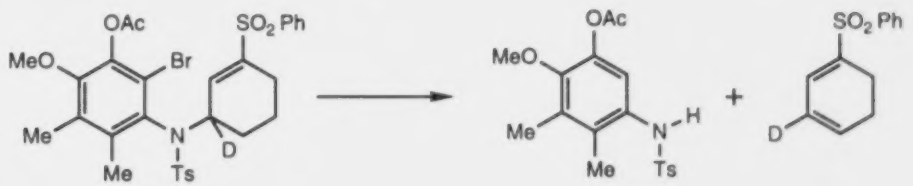


140b **144**

Triphenyltin hydride (0.028 mL, 0.11 mmol) in anhydrous benzene (2.5 mL) and AIBN (7.2 mg, 0.044 mmol) in benzene (2.55 mL) were each added over 10 h (double syringe pump) to a refluxing solution of crude **140b** (45.5 mg, 0.0687 mmol) in benzene (12

mL). The solution was refluxed a further 10 h, cooled, and evaporated. Flash chromatography of the residue over silica gel, using 2:1 hexanes–ethyl acetate, gave crude **144** (25.7 mg) as an off-white solid, which was recrystallized from CH_2Cl_2–hexanes to afford **144** (20.4 mg, 51%) as a single isomer. The material was a colorless, homogeneous (TLC, 2:1 hexanes–ethyl acetate) crystalline solid: mp 225–227°C; FT-IR ($CHCl_3$ cast) 1773, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.41 (m, 2 H), 1.66–1.88 (m, 1 H), 1.93 (s, 3 H), 2.03–2.18 (m, 3 H), 2.22 (s, 3 H), 2.40 (s, 3 H), 2.46 (s, 3 H), 3.24 (m, 1 H), 3.64 (s, 3 H), 3.80 (m, 1 H), 4.72 (dt, J = 12, 6 Hz, 1 H), 7.29 (d, J = 8 Hz, 2 H), 7.53 (d, J = 8 Hz, 4 H), 7.64 (d, J = 8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.04, 17.69, 18.26, 20.07, 21.27, 21.83, 28.28, 38.50, 59.88, 60.92, 62.32, 125.54, 127.68, 128.26, 129.36, 130.01, 131.71, 132.21, 133.77, 135.71, 137.33, 138.58, 138.70, 144.15, 148.92, 167.39; exact mass, m/z calcd for $C_{30}H_{33}NO_7S_2$ 583.1699, found 583.1691. Anal. Calcd for $C_{30}H_{33}NO_7S_2$: C, 61.73; H, 5.70; N, 2.40; S, 10.98. Found: C, 61.46; H, 5.66; N, 2.41; S, 10.91.

Fragmentation of *N*-(3-Acetoxy-2-bromo-4-methoxy-5,6-dimethylphenyl)-*N*-[1-deutero-3-(phenylsulfonyl)-2-cyclohexenyl]-4-methylbenzenesulfonamide (major isomer, 141a).



141a **117** **143**

Triphenyltin hydride (0.21 mL, 0.82 mmol) in anhydrous benzene (5 mL) and AIBN (47 mg, 0.29 mmol) in benzene (5 mL) were each added over 10 h (double syringe pump) to a refluxing solution of **141a** (376.0 mg, 0.567 mmol) in benzene (50 mL). The solution was refluxed a further 10 h, cooled, and evaporated. Flash chromatography of the residue over silica gel, using 4:1 hexanes–ethyl acetate, to elute **143**, and then 2:1 hexanes–ethyl acetate, to elute **117**, gave **143** (49.6 mg, 39%) as a white, homogeneous (TLC, silica, 2:1 hexanes–ethyl acetate) solid: mp 92–93.5°C; FT-IR ($CHCl_3$ cast) 1303, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.32 (m, 4 H), 6.08 (m, 1 H), 7.03 (s, 1 H), 7.48–7.67 (m, 3 H), 7.88 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.09, 22.83, 122.10*, 122.43*, 122.70**, 122.77*, 127.83, 129.14, 131.65, 133.18, 133.30, 136.27, 139.72; exact mass, *m/z* calcd for $C_{12}H_{11}O_2SD$ 221.0621, found 221.0614, and **117** (83.4 mg, 40%) as a white, homogeneous (TLC, silica, 2:1 hexanes–ethyl acetate) solid, identical to that prepared previously (^1H NMR, 200 MHz).

* Due to ^{13}C-D.

** Due to ^{13}C-H impurity.

Molecular Modelling and Molecular Mechanics[61]

Methods: Molecular modelling and force field calculations were carried out using the Insight-II program of Biosym Inc. The standard Biosym force field was used in all the energy calculations. For the non-bonded energy calculations a smooth cut off extending up to 15 Å was used.

The various conformations of compound **140** were modelled using the Builder module. The structures were then subjected to energy minimization using the DISCOVER module until the derivatives converged to 0.01 kcal/(mol·Å) or less.

Terminology: The labelling of atoms and rings is shown in Figures 5 and 6. The numbering corresponds to that used in the X-ray determination.

Results: In order to explain the difference in the observed reactivity of the two isomers of compound **140** towards attempted radical cyclization, and the related low yields for formation of compound **124**, the various rotational isomers were modelled using the Insight-II program. The X-ray crystal data available on the major isomer (**140a**) were used to generate a starting structure. A stereo display of this structure on the IRIS 4D/70GT workstation monitor showed that both the bromine on ring A and C(17) are *cis* with respect to the C(2)N-C(12) plane. One would initially infer that this arrangement is conducive to radical cyclization if the derived radical has a similar conformation. Since the experimental evidence indicates that this particular isomer does not undergo such a reaction, an extensive model study was carried out on the various possible conformers of compound **140**. First, the X-ray structure was subjected to energy minimization until all the derivatives converged to 0.01 kcal/(mol·Å) or less. The minimum energy conformation thus obtained is displayed in Figure 5. Then ring A

was rotated about its N-C bond by 180°, and ring C was also rotated by 180° about the N-C(12) bond. The conformation thus obtained is similar to the structure of Figure 5 except for two important factors. (1) Ring B is now *trans* to both the bromine atom and C(17). (2) The spatial arrangement at C(12) relative to the bromine atom is quite different. This structure was then subjected to energy minimization until all the derivatives converged to 0.01 kcal/(mol·Å) or less, as before. The conformation thus obtained is displayed in Figure 6. In order to ensure that the conjugate gradient minimization converged to the global minimum for this configuration the minimization was repeated with a different starting structure selected from a molecular dynamics run at 500 K for 7 ps, and the minimization procedure was repeated. This also converged to the same conformation. This procedure was then repeated for the major isomer; it also converged to a unique conformation. It is found that the major isomer is the most stable of all the possible rotational isomers. The difference in energy between this and the minor one is ~3 kcal/mol.

Molecular mechanics calculations are incapable of providing an exact value for the rotational energy barriers between the various isomers. However, using a rigid rotor approximation, the energy barrier for all three bonds attached to the central nitrogen were estimated to be very high. The steric demand from the bulky substituents on rings A and C allows only a few stable conformations separated by high energy barriers. The rotation about the

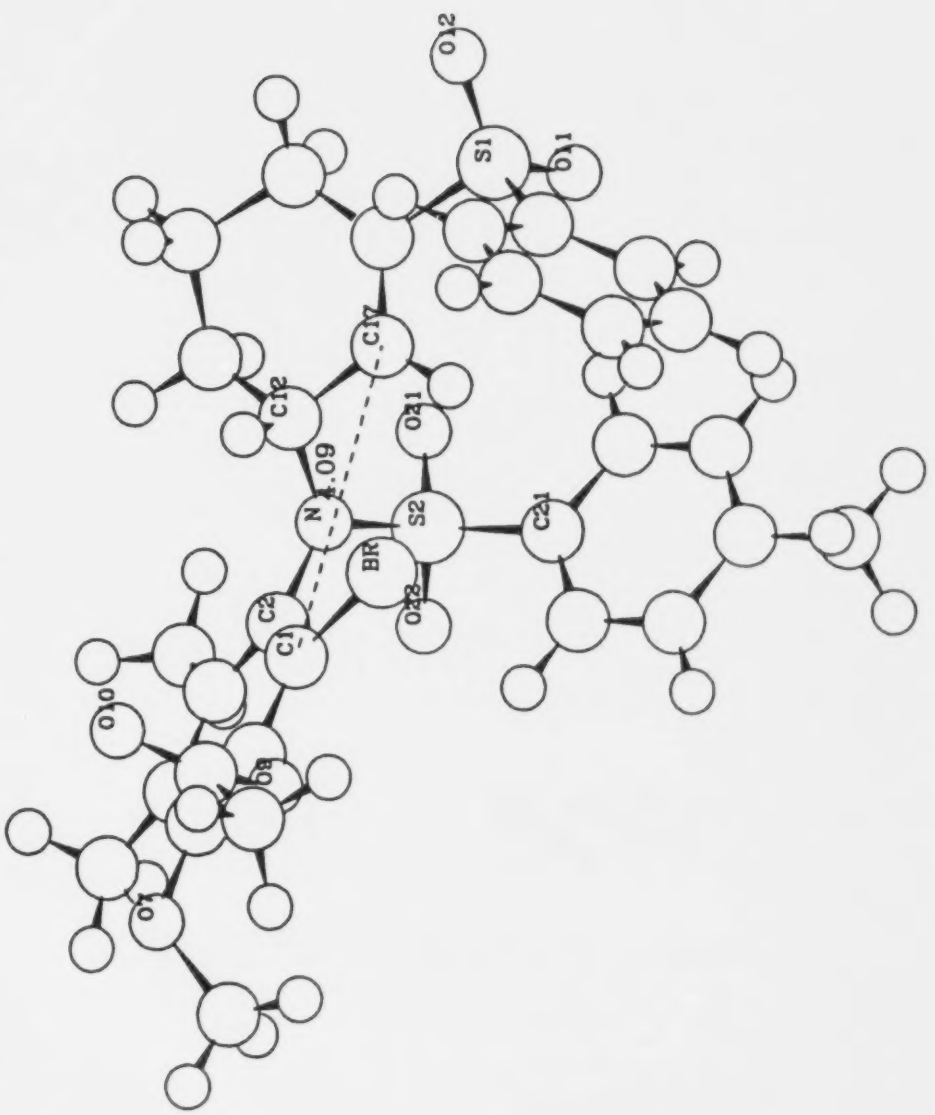


Figure 5. Calculated Conformation for Compound 140 (Major Isomer)

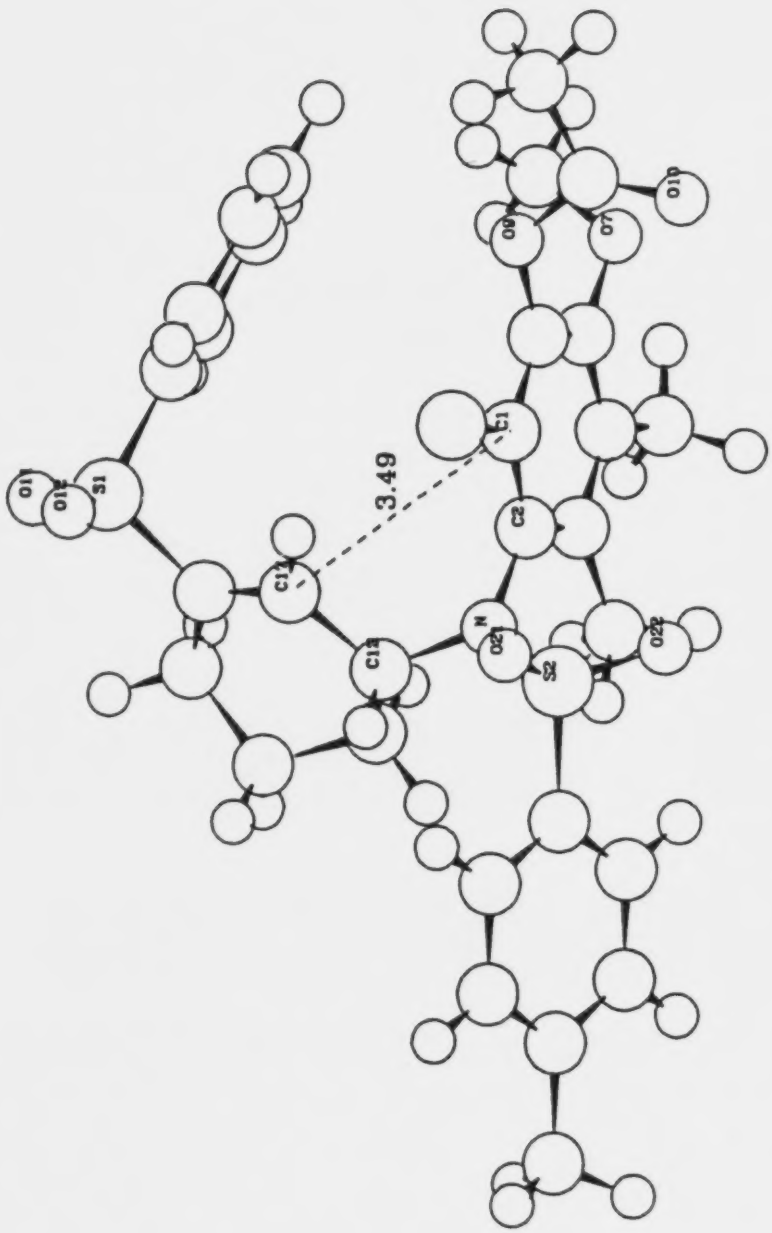


Figure 6. Calculated Conformation for Compound 140 (Second Isomer)

two N-C bonds and the N-S bond are very restricted, making the individual conformers exist as distinct and separable isomers.

In order to confirm this observation molecular dynamics calculations were carried out at 500K for both the major and minor isomers. Even after 7 ps no interconversion was observed from one isomer to the other. This observation is consistent with the experimental evidence that the isomers do not interconvert under thermal conditions.

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61) Molecular modelling and molecular dynamics calculations were performed by Drs. Tomi Joseph and J. William Lown.

62) Figures 3 and 4 show only the essential features. The original figures 5 and 6, on which figures 3 and 4 are based, are given in the experimental section (p 117 - 118).

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Part II

Development of a Radical Route to Amino Acids

I INTRODUCTION

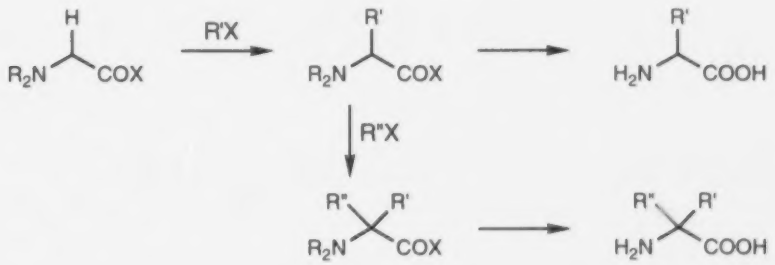
Methods of Amino Acid Synthesis

Traditional methods for the synthesis of α-amino acids have been extensively reviewed,[1-3] Much recent work has focussed on the application of established and newer methods to the asymmetric synthesis of amino acids.[4]

Most of the methods that have been used for the construction of amino acids can be classified into three general approaches. This brief review gives only one or two illustrative examples in each category.

a) Derivatization of Simple Amino Acids

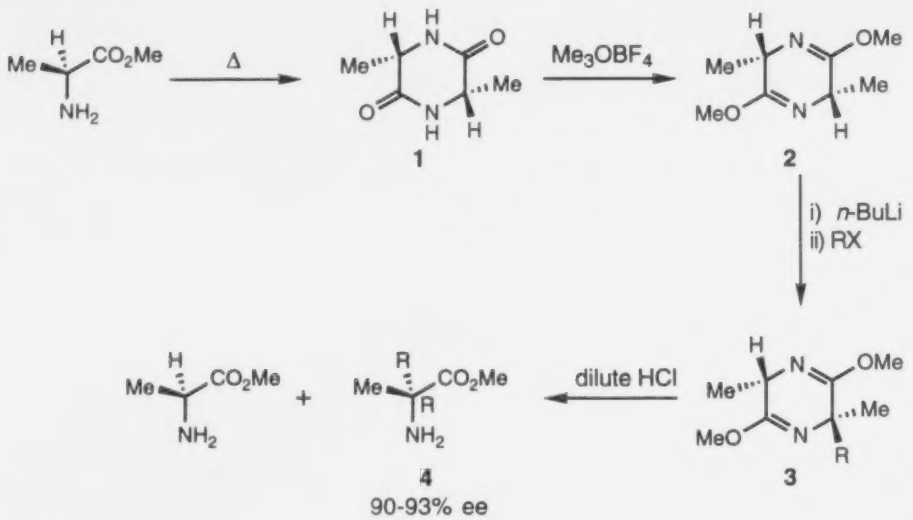
One of the ways in which amino acids have been prepared is the alkylation of simpler amino acids (usually glycine) as summarized in Scheme 1.



Scheme 1

Recent efforts, mostly by Schöllkopf,[5] have focussed on the asymmetric alkylation of bis-lactim ethers such as **2** (Scheme 2), which are prepared by coupling of L-alanine methyl ester, followed

by ether formation with trimethyloxonium tetrafluoroborate. Deprotonation at low temperature and alkylation gives preferential alkylation anti to the methyl group. Mild hydrolysis gives the (*R*)-amino acid methyl esters **4** with high levels of asymmetric induction.

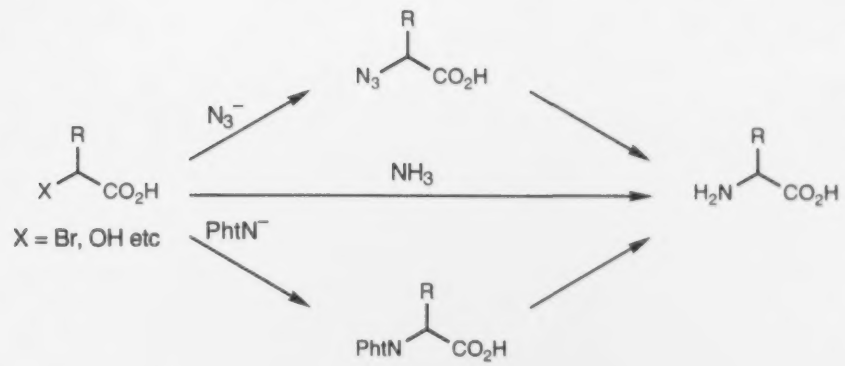


Scheme 2

b) Amination of α-Substituted Acids

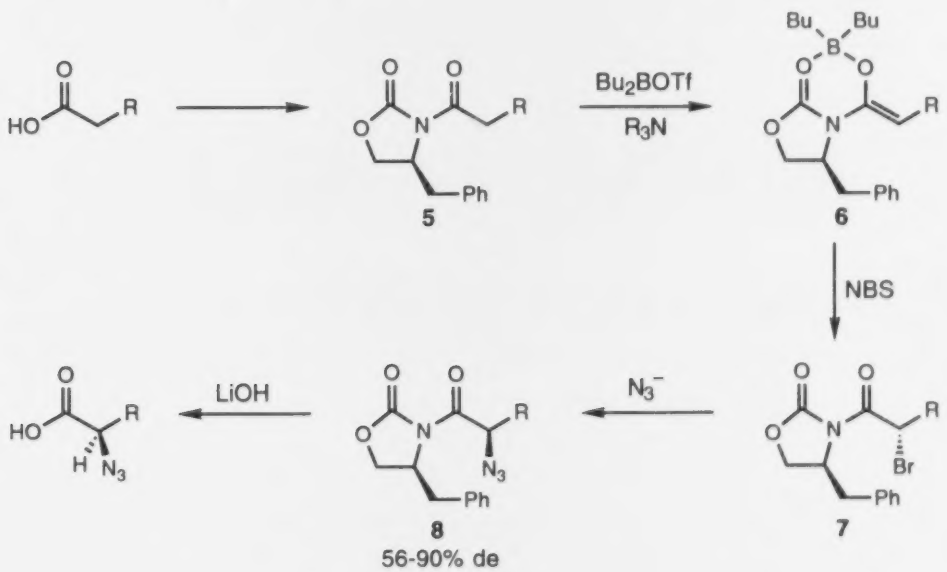
The second general category of amino acid synthesis is the displacement of α-functionalized amino acids (Scheme 3). The nitrogen can be introduced either by direct amination with ammonia or with activated amides (eg the Gabriel synthesis), or via the azide.

Again, recent developments in the application of these methods to asymmetric synthesis have been reported. Evans[6] has reported the bromination of chiral enolates **6** (Scheme 4) which are formed by condensation of carboxylic acids with a chiral amide and



Scheme 3

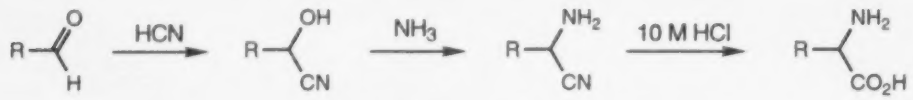
then enolization with dibutylboron triflate. The enolate is brominated, and the bromide displaced with azide to give **8** with generally high levels of asymmetric induction. Separation of the diastereomers by flash chromatography gives **8** in >98% diastereomeric excess. Hydrolysis gives (with recovery of the chiral auxiliary) the azido acids, which can easily be reduced to the corresponding amino



Scheme 4

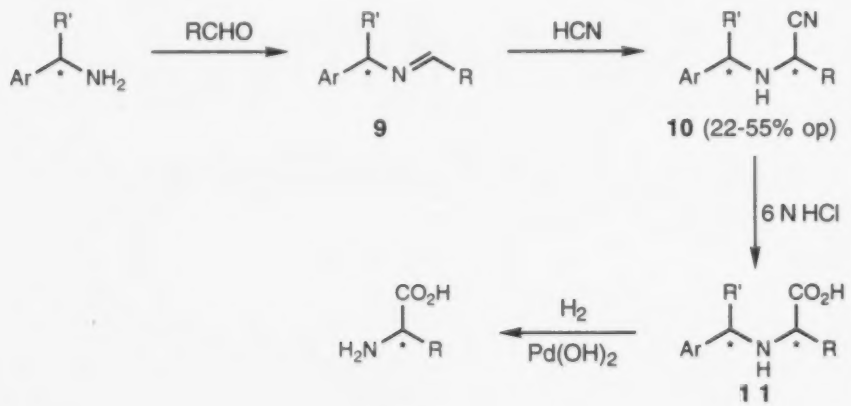
acids.

There are also a few reports of asymmetric induction in the Strecker synthesis, which has been one of the most widely applied methods for the assembly of amino acids. The sequence generally consists of conversion of an aldehyde into the cyanohydrin, displacement with ammonia, and hydrolysis (Scheme 5).



Scheme 5

The first asymmetric application was reported by Harada.[7] Generally, the aldehydes are first condensed with optically active amines to give chiral Schiff bases **9** (Scheme 6). Addition of HCN gives the α-amino nitrile **10** with moderate levels of asymmetric induction. Hydrolysis and catalytic hydrogenolysis then affords the optically enriched amino acids.



Scheme 6

c) Rearrangements

Finally, amino acids can be formed by rearrangements such as that originally described by Curtius[8] (Scheme 7). This protocol involves rearrangement of an acyl azide to form an isocyanate, which is hydrolyzed to give the amino acid.

Scheme 7

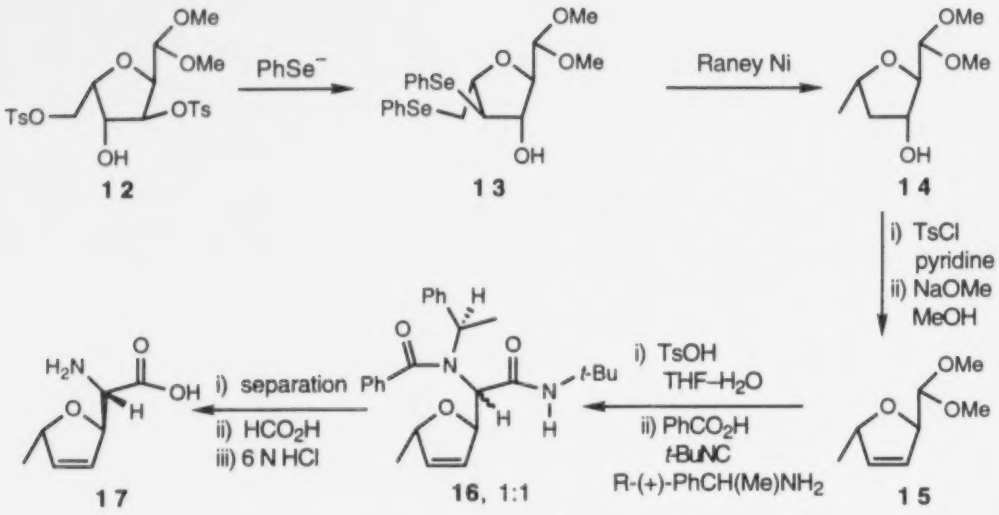
Although the Curtius rearrangement and related reactions were once extensively employed, they are now only rarely used as other, more convenient, methods have been developed.

d) Newer Methods of Amino Acid Synthesis

Several of the newer methods do not clearly fit into one of the above categories.

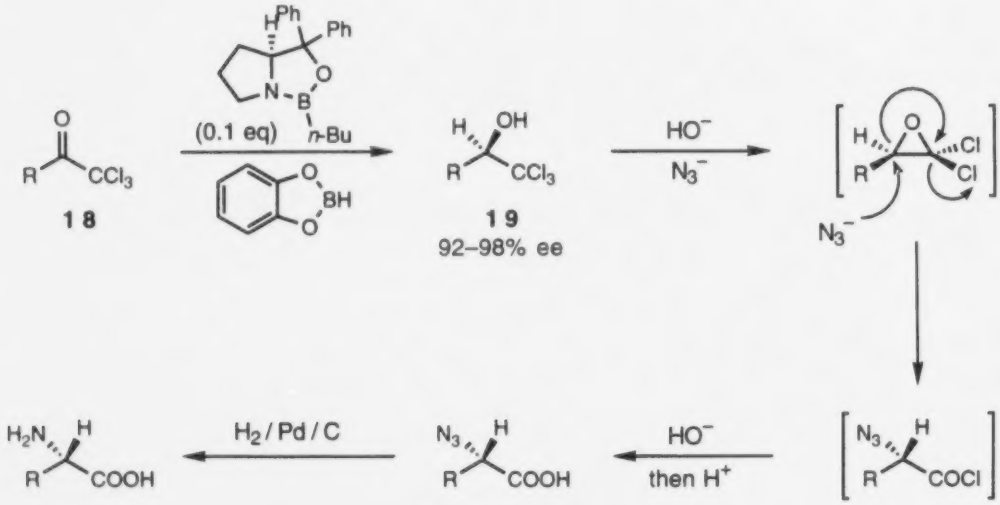
The Ugi four-component condensation is a 'one-pot' amino acid synthesis, in which both the amino and the carboxylic acid functionalities are introduced in one step. This approach has been used by Joullié, whose synthesis of the antibiotic furanomycin (**17**, Scheme 8) served also to correct the previously assigned stereochemistry of the natural product.[9] In this synthesis, the aldehyde derived from acetal **15** (available by the sequence shown from glucose derivative **12**[10]), is condensed with (*R*)-phenylethylamine to give the Schiff base. Further condensation with *t*-butyl isocyanide and benzoic acid gives a mixture of amides **16**, which are

separated and deprotected to produce (+)-furanomycin **17** and its α-epimer.



Scheme 8

Recently, Corey published an elegant synthesis of L-α-amino acids based on the enantioselective reduction of trichloromethyl

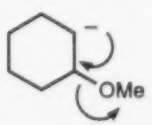


Scheme 9

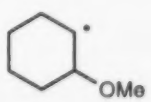
ketones **18** (Scheme 9).[11] The (*R*)-(trichloromethyl)carbinols **19** were treated with base to form the intermediate epoxides which were opened by azide ion to give, after hydrolysis, azido acids. These were converted by standard methodology to the corresponding amino acids.

Radical Techniques in Amino Acid Synthesis

To date, little work has been reported on the application of radical reactions to the synthesis of amino acids. One of the advantages of such techniques is that they may allow the formation of amino acids not easily accessible by other methods. For example, an α-functionalized carbon moiety such as **20** could not be introduced by ionic means, as it would eliminate the adjacent substituent. Radical **21**, however, would be expected to add to double bonds without elimination.



20



21

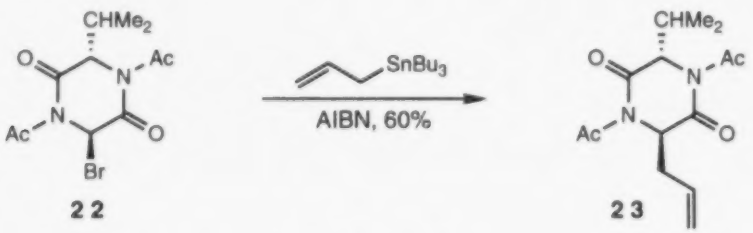
Most of the reports in this area involve the modification of pre-formed amino acids, either by generation of a radical within the amino acid, or by intermolecular addition of other radicals to unsaturated amino acids.

a) Addition of Radicals Derived From Amino Acids

Radicals generated from amino acids can add to double bonds within the amino acid, or intermolecularly to activated olefins. These radicals can be in the α position (thereby generating the α stereogenic center) or elsewhere in the molecule (often in the β position).

There are several reports of the addition of radicals in the α position to allyl tin compounds. Some recent examples show high levels of diastereoselectivity.

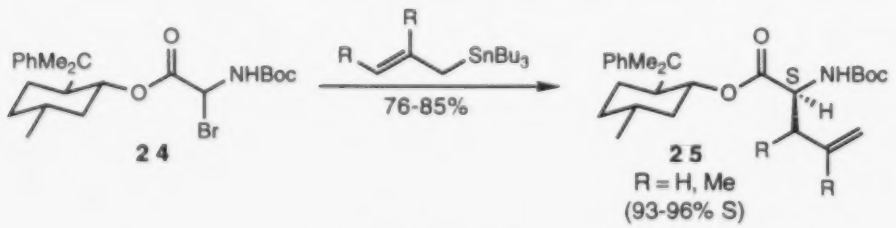
For example, Easton[12] has reported the addition of the radical derived from bromide **22** (Scheme 10) to allyltributyltin as giving only the isomer shown.



22 **23**

Scheme 10

Hamon[13] has also reported the use of a chiral auxiliary to give protected amino acids **25** (Scheme 11) with high levels of asym-



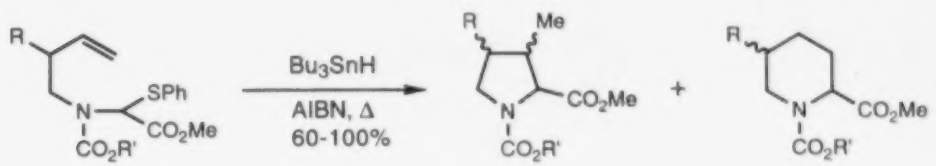
24

25
R = H, Me
(93-96% S)

Scheme 11

metric induction.

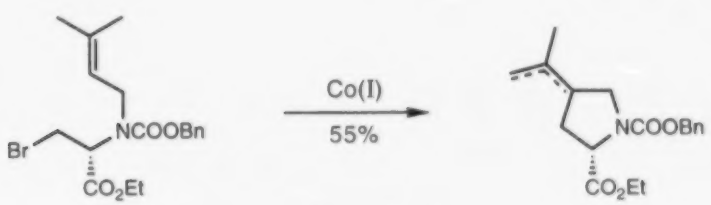
In suitably substituted amino acids, radicals can also add intramolecularly to give cyclic derivatives. For example, the radicals generated from phenyl thioethers **26** (Scheme 12) give mixtures of the 5-exo and 6-endo cyclization products.[14]



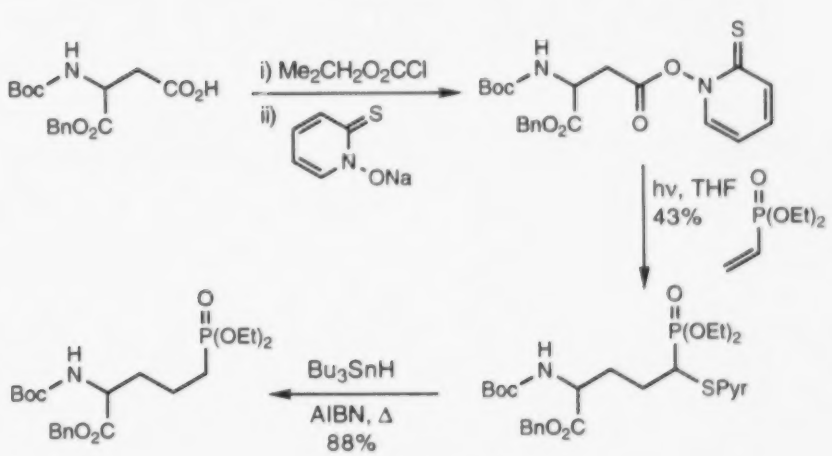
26 **27** **28**

Scheme 12

Radicals generated in the β position of amino acids react



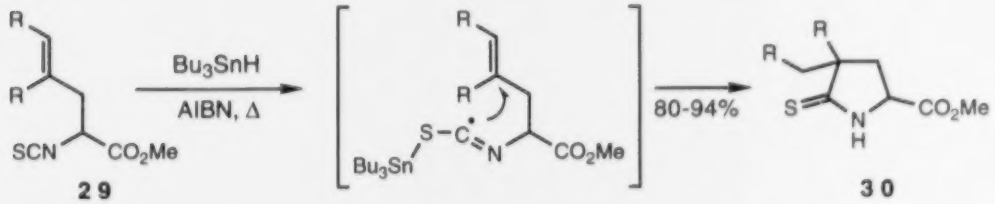
Scheme 13



Scheme 14

similarly. Baldwin[15] has reported the cobalt-mediated cyclization of radicals generated from β-bromo amino acids (Scheme 13), while Barton[16] has prepared phosphonates of amino acids by radical decarboxylation and intermolecular addition (Scheme 14).

In an unusual variation, the radical generated from thiocyanate **29** (Scheme 15) cyclizes to give, on hydrolysis, thioamide **30**.[17]

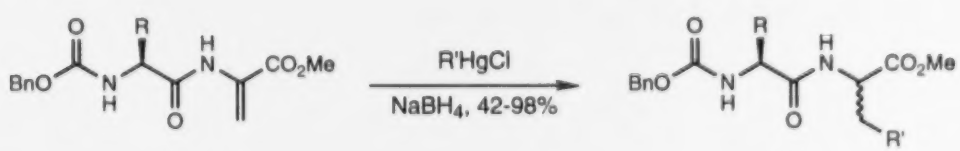


29 **30**

Scheme 15

b) Radical Addition to Unsaturated Amino Acids

The intermolecular addition of radicals to dehydroalanine derivatives has also been reported. The first such report was Crich's[18] addition of radicals generated by reduction of mercuric halides to dipeptides **31** (Scheme 16) to give the alkylated derivatives **32** in good yields but with generally low levels of diastereoselectivity.

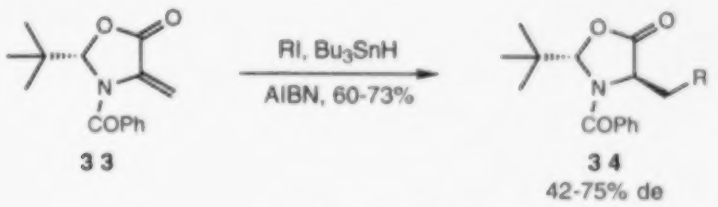


31 **32**
1-28% de

Scheme 16

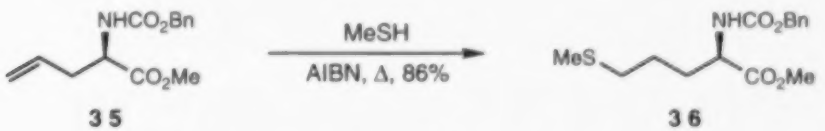
More recently, Beckwith[19] has reported radical addition to

dehydroalanine **33** (Scheme 17). In this cyclic case, addition occurred with higher levels of diastereoselectivity.



Scheme 17

Finally, Broxterman[20] has found that addition of sulfur radicals to optically active unsaturated amino acids such as **35**, thereby forming homomethionine derivative **36** (Scheme 18), occurs with little (<1%) loss of optical activity.



Scheme 18

Clearly, the development of radical methods for the synthesis of amino acids is at a very early stage, but this is an area which will likely attract considerable attention in the future.

Previous Studies of Radical Addition in Amino Acid Synthesis

Efforts in this laboratory to develop a general route to amino acids using radical chemistry began with attempts to add carbon radicals to dehydroamino acid substructures.[21]

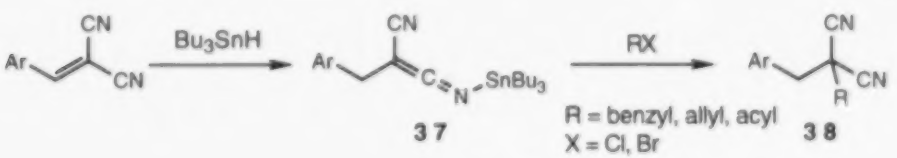
The first routes examined involved addition to imine or oxime

double bonds (Scheme 19).

Scheme 19

Although radicals are known to add to imines[22] and oximes,[23] none of the potential amino acid precursors examined proved to be reactive.

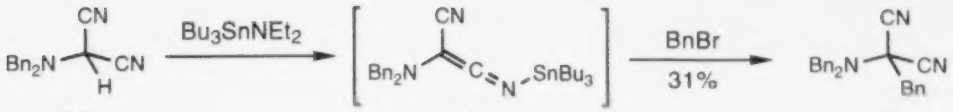
Another approach was based on Neumann's observation that *N*-stannyl ketenimines **37** react with certain alkyl halides to give dinitriles **38** (Scheme 20).[24]



Scheme 20

Although an ionic mechanism was proposed, it was felt that a radical mechanism could operate.[21] On this basis, nitriles **39** and **41** (Schemes 21 and 22) were prepared, in the hope that ketenimine formation and alkylation would provide products which could easily be hydrolyzed to amino acids.

Scheme 21



41 **42** **43**

Scheme 22

Nitrile **39** could not be converted into the desired *N*-stannyl ketenimine **40**. Dinitrile **41**, however, was easily converted into the required intermediate, which gave a modest yield of **43** on heating with benzyl bromide.

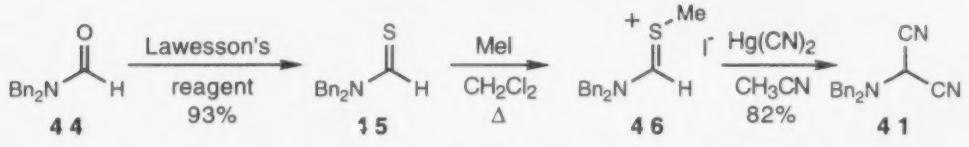
It remained to optimize the reaction conditions, develop a procedure for hydrolysis of the adduct, and to determine if the reaction does indeed follow a radical mechanism.

II DISCUSSION

Our work in the area of amino acid synthesis began with a re-examination of the reaction developed earlier[21] as a potential radical route to amino acids.

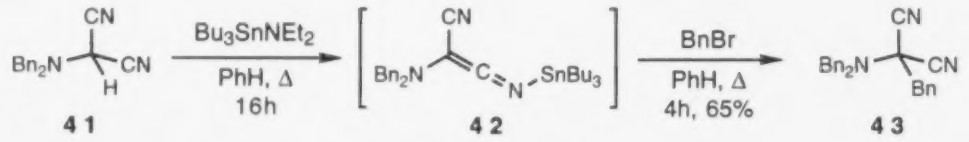
Addition of Carbon Radicals to *N*-Stannyl Ketenimines

Dinitrile **41** was prepared according to the procedure reported previously (Scheme 23).[21] Thioamide **45**, was made from the corresponding formamide, and then methylated on sulfur. Finally, displacement with cyanide gave the required material.



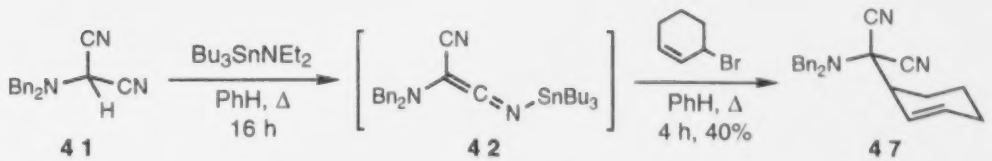
Scheme 23

Modification of the reaction conditions for the formation of *N*-stannyl ketenimine **42** and for the subsequent alkylation led to an improved yield of the alkylated dinitrile **43** (Scheme 24). Although **42** was not isolated, its intermediacy was established by its characteristic infrared spectrum.



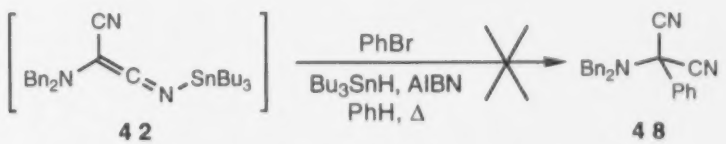
Scheme 24

A similar reaction with 3-bromocyclohexene gave the allylic derivative **47** (Scheme 24).



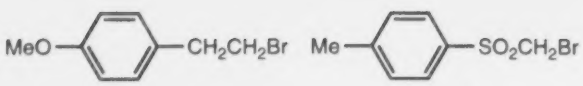
Scheme 25

Earlier studies[25] had shown that ketenimine **42** did not react with bromobenzene, and in fact we found that even when heated in the presence of AIBN and tributyltin hydride – usual conditions for the generation of aryl radicals – no arylation product **48** (Scheme 26) was formed.



Scheme 26

We also attempted to add the primary bromide **49**,[26] and the electrophilic radical generated from *p*-toluenesulfonylmethyl bromide **50**.[27] In neither circumstance was any alkylated dinitrile observed. In these cases, together with substantial quantities of unchanged **41**, we isolated small amounts (3–25%) of the hydrolysis product **51**, apparently formed by attack of water on intermediate **42**. When a mixture of ketenimine **42** and bromide **50** was irradiated (sunlamp) instead of heated, the amount of **51** increased to 43%.



49 **50** **51** **52**

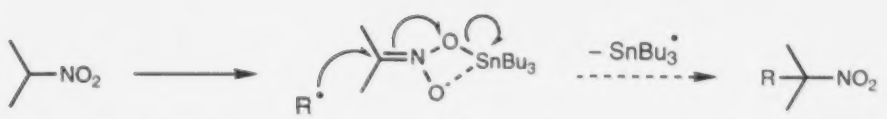
Treatment of ketenimine **42** with the 2-propyl radical, formed by Barton's radical decarboxylation[28] of **52**, also gave a small amount of **51**, and no product of radical addition.

Finally, in order to determine conclusively if the reaction followed a radical mechanism, we repeated the benzylation (Scheme 24) using benzyl phenylselenide[29] in place of benzyl bromide in the second step. If the reaction truly followed a radical mechanism, we would expect the selenide to react in a similar manner to the bromide. However, in this experiment benzylation was not observed (TLC), and only the starting dinitrile was recovered.

These results suggested that the reaction did not follow a radical mechanism. We therefore sought other amino acid templates onto which we could add carbon radicals.

Addition of Carbon Radicals to Other Acceptors

A literature report[30] described the synthesis of the nitro-tin adduct **53** by stannylation of 2-nitropropane (Scheme 27). We felt that if a carbon radical could be induced to add as shown in the Scheme, we would have a general method of radical alkylation. If the reaction could be extended to an appropriately substituted analogue of **53**, then reduction of the resulting nitro compound could lead to amino acids.



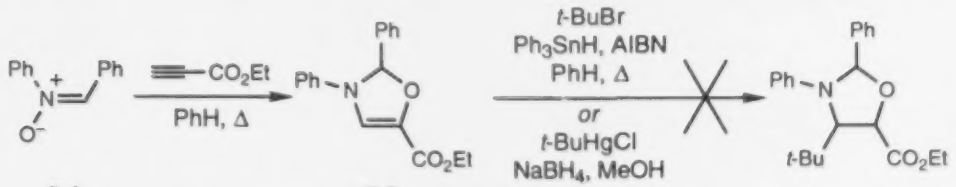
53

Scheme 27

Unfortunately, when **53** was treated with benzyl bromide, even in the presence of AIBN and tributyltin hydride, addition was not observed.

The next template we examined was the 4-oxazoline **55** (Scheme 28), which is available from nitrone **54** by a general literature procedure.[31] If a radical could be added to the double bond in the manner indicated, thereby generating a stabilized, capto-dative radical,[32] we would have a system which could be hydrolyzed to give an amino acid derivative.

However, treatment with *t*-butyl bromide under the usual radical conditions gave no evidence of radical addition. The IR spectrum of the crude reaction mixture suggested the presence of a saturated ester, however the ^{1}H NMR showed little, if any, *t*-butyl incorporation. The mass spectrum indicated that there might be some addition of the triphenyltin radical[18b] to **55**.



54 **55**

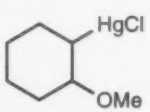
Scheme 28

In order to avoid the use of tin radicals, we attempted to

generate the radical from the corresponding mercuric chloride[33] by reduction with sodium borohydride. When the reaction was done in methanol, however, there appeared to be addition of the solvent to the double bond. In a separate test, the starting 4-oxazoline **55** was found to be decomposed by methanolic sodium borohydride.

Alternatively, we attempted reduction of the mercuric salt using tetrabutylammonium borohydride, thus allowing the use of aprotic solvents. Still, no radical addition was observed.

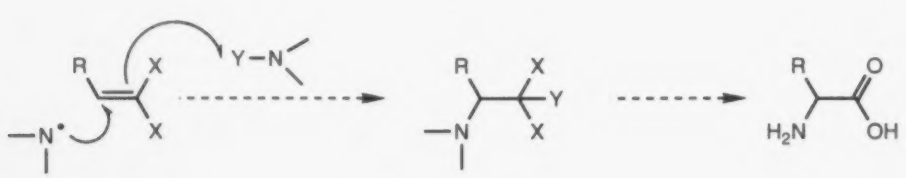
We then attempted a similar addition using the secondary (and presumably less hindered) mercuric chloride **56**.[34] Again, the mass spectrum of the crude reaction mixture showed no radical addition.



56

Intermolecular Addition of Nitrogen Radicals

We then turned our attention to the addition of nitrogen radicals to the carbon backbone of potential amino acids, according to the general principle outlined in Scheme 29. The groups X and Y would be chosen in order to stabilize the radical formed by the

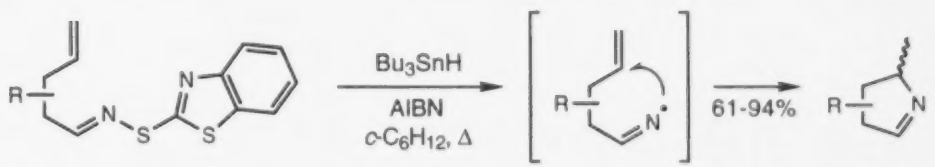


Scheme 29

initial addition, and to allow transformation into the eventual carboxylic acid.

The first nitrogen radicals we examined were the iminyl radicals reported by Zard[35] to undergo rapid radical cyclization, in contrast to aminyl radicals, which often must be protonated or complexed before they will add to unactivated double bonds.

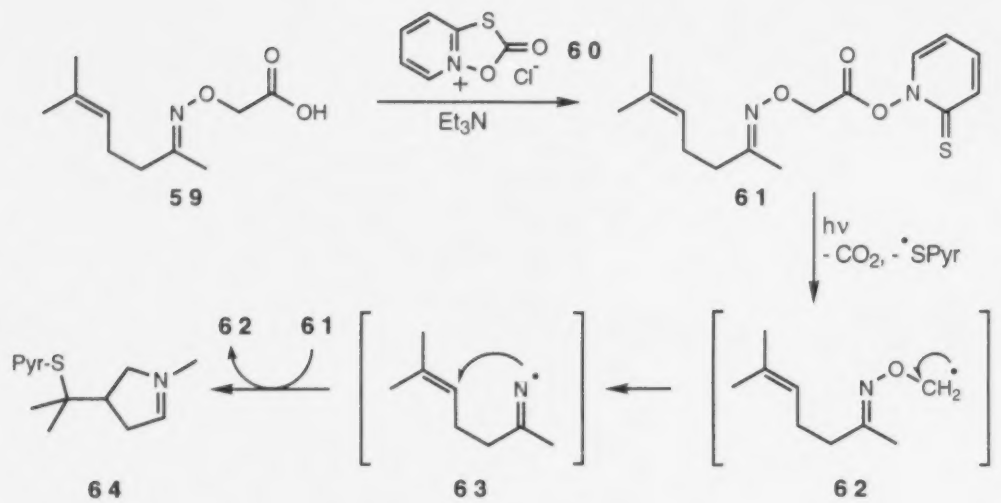
The first synthetically useful method reported for the generation of these radicals was the stannane-induced decomposition of sulphenylimines **57**, themselves available from the corresponding ketones or aldehydes (Scheme 30).[35a,b] Radical cyclization of the so-produced iminyl radicals gave good yields of pyrrolines **58**.



57 **58**

Scheme 30

A later report[35c] described the generation of these radicals using a modificaton of Barton's decarboxylation methodology.[28] Here, the radicals were generated from *O*-carboxymethyl oximes **59** by irradiation of their *N*-hydroxy-2-thiopyridone esters. Fragmentation of the initially formed species **62** gives the iminyl radical **63** which, again, cyclizes onto the double bond. In the absence of hydrogen donors, the resulting radical reacts with thiopyridone **61** to give **64** instead of the simple pyrroline.

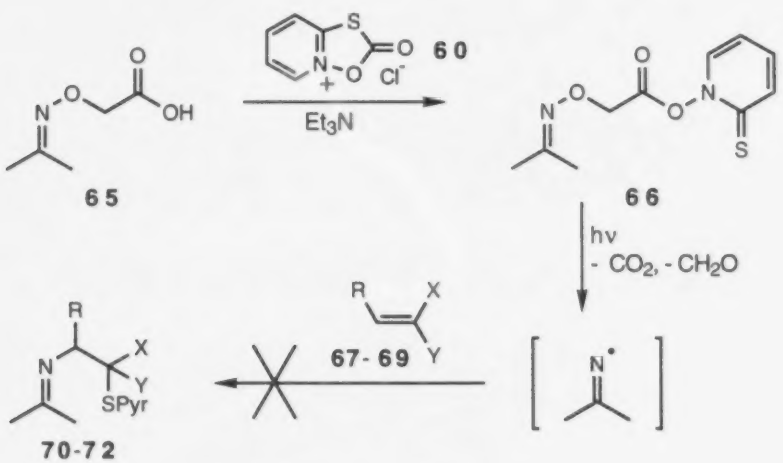


59 61 64 63 62

Scheme 31

To date, there are no reports of intermolecular addition of these iminyl radicals to double bonds. However, we felt that such radicals might be induced to add to sufficiently activated olefins.

We chose acid **65**,[36] (Scheme 32) derived from acetone oxime,



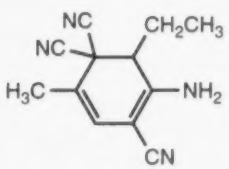
65 66 70-72

67, **70**: R = Et, X = Y = CN
68, **71**: R = Et, X = CN, Y = OCH_3
69, **72**: R = H, X = OEt, Y = H

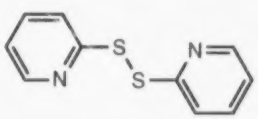
Scheme 32

as the radical precursor. Treatment with salt **60**[28] gave crude **66**, which was not isolated, but was irradiated (300W tungsten lamp, in refluxing dichloromethane) in the presence of olefins **67–69**.

The first olefin used was dinitrile **67**.[37] When irradiated in the presence of **66** as described above, no product of radical addition was observed. The only identified product was a dimer of **67**, tentatively assigned structure **73** on the basis of its NMR spectra. It is likely that **73** was formed by excitation of the monomer, and cycloaddition of the resulting substance with another molecule of **67**.



73



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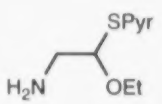


75

Since the dinitrile seemed to be too reactive to be of use, we next prepared the methoxyacrylonitrile **68**. This material was available by Wittig reaction of propionaldehyde with (cyanomethoxymethyl)triphenylphosphonium bromide.[38]

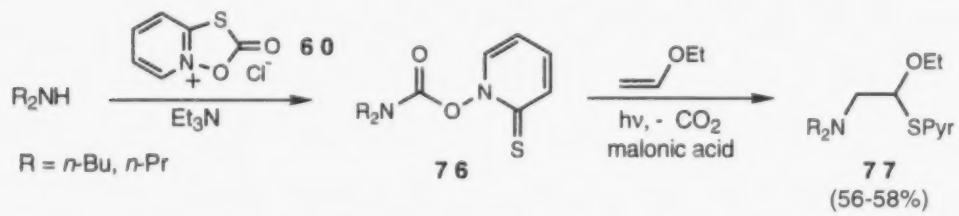
Once again, when a mixture of **66** and **68** was irradiated, no addition product was observed. This time, the only product identified was dipyridyl disulfide **74**.[39]

Finally, we attempted the irradiation of **66** in a 50% solution of ethyl vinyl ether (**69**) in dichloromethane. Although we did not isolate any **72**, in addition to a substantial amount of disulfide **74**, we did isolate a small amount (8%) of amine **75**, presumably

formed by hydrolysis of the initially formed imine.

The exceeding low yield of addition product, even when the radical acceptor was used as solvent, seemed to indicate that these iminyl radicals were not reactive enough to be of practical use for our purposes.

Newcomb[40] has reported that aminium cation radicals, generated from *N*-hydroxypyridine-2-thione carbamates **76** (Scheme 33) in the presence of malonic acid, add to enol ethers to produce sulfides **77** (or the corresponding desulfinated material if the reaction is performed in the presence of a hydrogen donor).

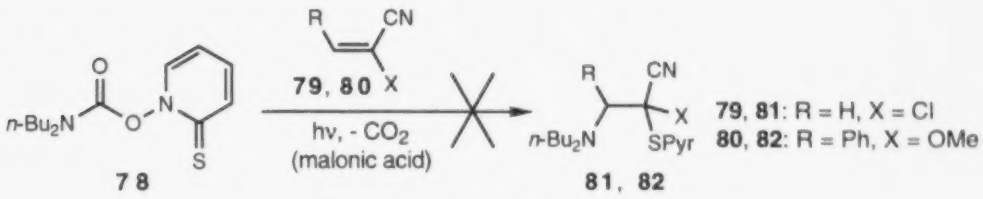


Scheme 33

Although Newcomb's reaction again required the use of very high concentrations of the enol ether, we felt that if we used an acceptor that would result in the formation of a capto-dative radical, we might be able to perform the reaction at more useful concentrations.

Our first attempt was the addition of the dibutylaminyl radical, generated by irradiation of **78**,[40a] to 2-chloroacrylonitrile in the presence of malonic acid (Scheme 34). Upon irradiation with a 300 W tungsten bulb the solution rapidly darkened, turning red and then dark brown. No addition product **81** was observed, while

some carbamate **78** was recovered unchanged.

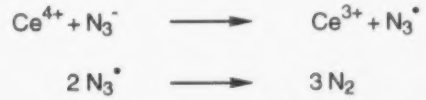


Scheme 34

Since 2-chloroacrylonitrile appeared to be too prone to polymerization under the reaction conditions, we tried using methoxyacrylonitrile **80**[41] as the radical acceptor. Although all of the carbamate was consumed in this case, the only identified product was disulfide **74**.

At this stage we turned to another idea that eventually proved fruitful. Some twenty years ago, Trahanovsky[42] reported the addition of azide radicals to double bonds.

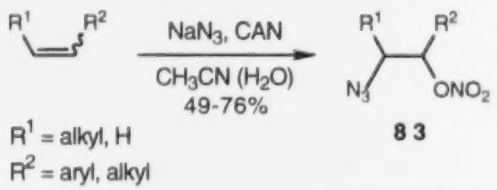
It had been known for some time[43] that metal azides are oxidized quantitatively by ceric compounds to give nitrogen. The intermediacy of the azido radical has been proposed, and the mechanism outlined in Scheme 35 has been suggested.



Scheme 35

Trahanovsky found that the evolution of nitrogen is completely suppressed by the addition of olefins. A variety of alkyl and aryl substituted olefins were able to trap the initially formed

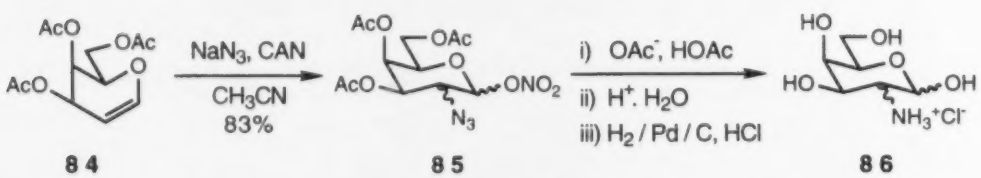
azide radical to give azido nitrates **83** (Scheme 36). Interestingly, the reaction failed when electron deficient olefins (R^1 or R^2 = COR, CO_2R) were used.



Scheme 36

The first synthetic application of this reaction was Lemieux's[44] azidonitration of 1,2-anhydro sugars (Scheme 37). In the first reported example, tri-*O*-acetyl-D-galactal **84** was treated with sodium azide and ceric ammonium nitrate to give a mixture of azido nitrates **85**. The major components had the azide in the equatorial conformation, with the galactose to talose ratio greater than 9 to 1.

A two-step hydrolysis of the nitrate and reduction of the azide gave the 2-amino-2-deoxy sugar **86**.

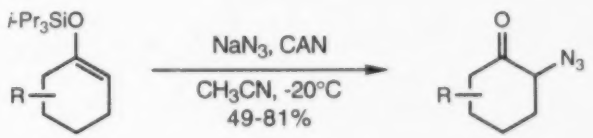


84 **85** **86**

Scheme 37

This reaction sequence has provided a facile and convenient method for the preparation of these amino sugars, which has been used extensively in the ensuing years.[45]

Very recently, Magnus[46] published an account of the formation of α-azido ketones **88** by treatment of triisopropylsilyl enol ethers **87** under conditions similar to those used for the azidonitration of anhydro sugars. In this case, the initial adduct is evidently hydrolyzed under the reaction conditions to give the ketones. The reaction was also reported for one acyclic enol ether, giving the corresponding α-azido ketone, but in substantially lower yield than in the cyclic cases.



87 **88**

Scheme 38

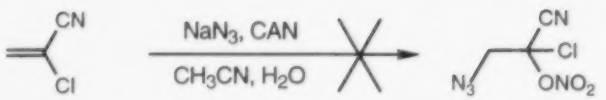
An earlier report[47] described one example of a very similar reaction, but using a *t*-butyldimethylsilyl enol ether. In this case, difficulty was encountered due to competing hydrolysis of the enol ether in the acidic (CAN) reaction medium.

We felt that the azidonitration methodology might prove useful to us if we chose olefins substituted in such a way that the products could be hydrolyzed to amino acids.

Azidonitrations

We first attempted the azidonitration of 2-chloroacrylonitrile. When treated under the conditions described by Trahanovsky,[42] considerable nitrogen evolution was observed, and no azido nitrate

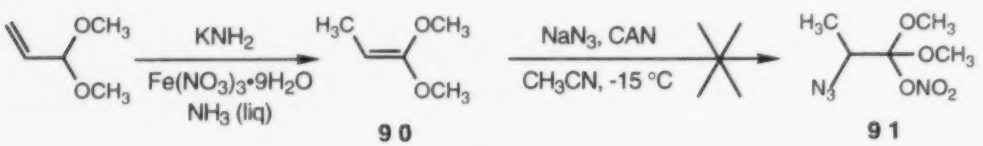
89 (Scheme 39) was isolated.



79 **89**

Scheme 39

We next tried using the less electrophilic ketene acetal **90**,[48] prepared by isomerization of acrolein dimethyl acetal (Scheme 40). Although nitrogen evolution appeared to be suppressed when **90** was added to a mixture of sodium azide and ceric ammonium nitrate, and the starting material was consumed, the ^{1}H NMR spectrum of the crude reaction mixture showed no evidence of azido nitrate **91**.



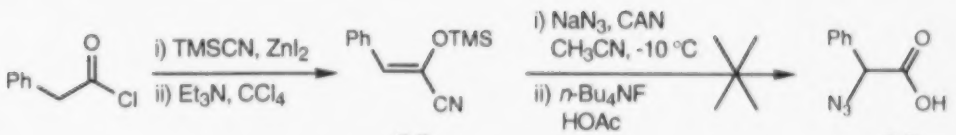
90 **91**

Scheme 40

We also examined the acrylonitriles **92**[49] and **94**[50] (Schemes 41 and 42), each available from the corresponding acid chlorides by treatment with TMSCN[51] to give the acyl cyanides, and then enolization and protection.

Silyl enol ether **92** was subjected to the azidonitration conditions, and the resulting mixture was treated with tetrabutylammonium fluoride in order to hydrolyze the resulting intermediates. The resulting material, however, did not contain any azido acid **93**

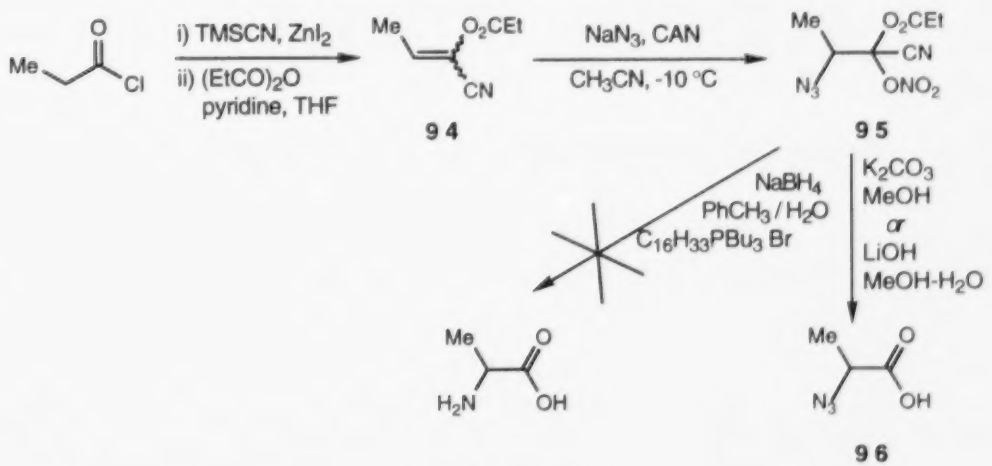
(^{1}H NMR, 200 MHz).



Scheme 41

We now feel, for reasons that will be described later, that this last sequence may have failed because the silyl enol ether is conjugated to the phenyl group. It is also possible that the trimethylsilyl group is too sensitive to withstand the reaction conditions, and that other silicon protective groups may prove more suitable.

Similar treatment of enol ester **94**, gave a crude mixture which appeared to contain some azido nitrate **95**, and also some hydrolyzed azido acid **96** (Scheme 42), along with significant quantities of unreacted starting material. When the crude mixture was hydrolyzed with methanolic potassium carbonate or lithium

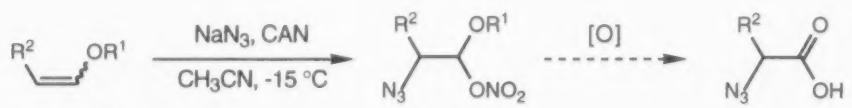


Scheme 42

hydroxide, a low yield (30–45%) of what appeared (on the basis of ^{1}H NMR) to be very impure azido acid **96** was isolated. However, when this material was hydrogenated over palladium, none of the corresponding amino acid was observed by comparison with an authentic sample.

We also tried to hydrolyze and reduce the material directly to the amino acid by treatment with sodium borohydride under phase transfer conditions.[52a] These conditions are reported to reduce azido acids to amino acids, and should also serve to reduce the ester, thereby liberating the acid functionality. However, once again, no alanine was formed.

We next attempted the azidonitration of several simple enol ethers (Scheme 43), in the hope that, like Lemieux's anhydro sugars, these would give stable products. We would then have to oxidize the resulting species to the carboxylic acids.



69, 97, 98 **99-101**

69, 99: R^1 = Et, R^2 = H
97, 100: R^1 = Me, R^2 = CH_2Ph
98, 101: R^1 = R^2 = CH_2CH_2

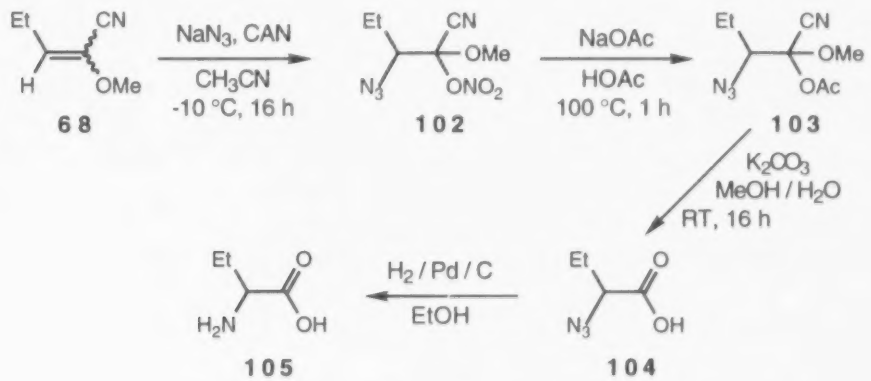
Scheme 43

The first enol ether we examined was ethyl vinyl ether (**69**). Although the reaction appeared to be very clean (TLC), and the chromatographed product was pure (^{1}H NMR), the yield of **99** was disappointingly low (8–9%). Clearly, this simple azido nitrate was

not as stable as those derived from anhydro sugars.

We also tried using the benzylic enol ether **97**, and 2,3-dihydrofuran (**98**) in the reaction, but both of these gave complicated mixtures after the azidonitration. This was particularly surprising in the case of dihydrofuran because of the analogies in carbohydrate chemistry.

Finally, we tried using the methoxyacrylonitrile derivative **68**. The first time we attempted this reaction, we were very pleased to obtain, after chromatography, a 40% yield of the azido nitrate **102** (Scheme 44). We were able to convert this material, using a variation of the route developed by Lemieux,[44] into 2-aminobutyric acid, **105**.



Scheme 44

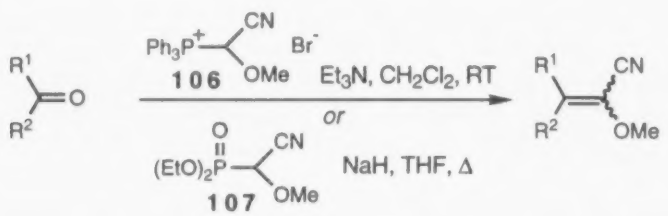
To our disappointment, when we attempted to repeat the azidonitration, we were unable to reproduce the yield and level of purity. After some experimentation, however, we were able to refine the reaction conditions such that it was possible to obtain an acceptable yield of azido acid **104** (50% overall yield for the three

steps from **68**). In order to obtain optimum yields of **104**, it was necessary to perform the three steps in sequence, without isolation and purification of the intermediates.

The azido acid was transformed into the amino acid by known methodology.[52b]

We now had what appeared to be a viable route to amino acids using radical methodology, and starting from simple materials. We next prepared a variety of methoxyacrylonitriles, in order to evaluate the scope of the reaction. Table 3 shows the olefins that were prepared for this purpose.

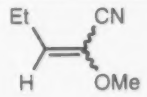
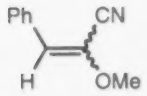
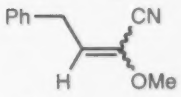
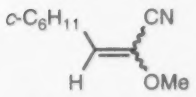
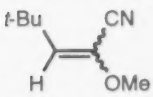
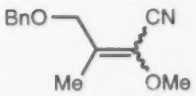
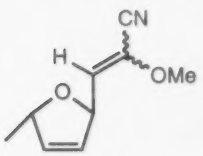
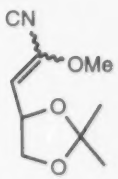
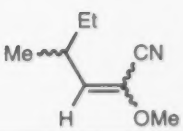
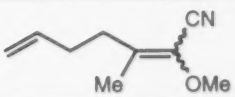
The required olefins were made from the corresponding aldehydes or ketones according to the general sequence outlined in Scheme 45. Two different methods for this conversion have been published, one using the phosphonium salt **106**[38] (Method A) and the other using phosphonate **107**[41] (Method B).



Scheme 45

We found the first method to be superior for the conversion of the more volatile aldehydes, in particular propionaldehyde was too volatile, and the resulting olefin **68** too unstable, to be prepared efficiently by the phosphonate method.

Table 3. Synthesis of Methoxyacrylonitriles

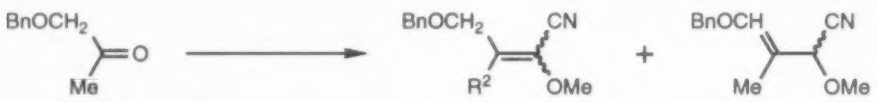
Methoxyacrylonitrile		Yield (method)[a]	Isomer Ratio[b]
	**68**	77% (A)[c]	5.8 : 1
	**80**	49% (A)	4.6 : 1
	**108**	78% (A)	4.5 : 1
	**109**	45% (A) 85% (B)	2.3 : 1 1.8 : 1
	**110**	<5% (A) 81% (B)	–– 1.8 : 1
	**112**	67% (B)[d]	1.7 : 1
	**136**	8-9% (A/B)[e]	f
	**138**	59% (B)[g]	>6 : 1
	**143**	87% (B)	1.7 : 1
	**167**	78% (B)	1 : 1

a) Method A: $Ph_3PCH(OCH_3)CN$ Br, Et_3N, CH_2Cl_2; Method B: $(EtO)_2P(O)CH(OCH_3)CN$, NaH, THF, Δ. b) Determined by ^1H NMR. c) Contains ca. 5% CH_3OCH_2CN. d) Also isolated 11% of the double bond isomer ***113****. e) From the acetal* ***15****. f) Only one isomer isolated in a pure form. g) 7% one isomer, 52% other isomer, 85% pure; remainder of material is mixture of other isomers.*

However, the second method gave much better yields, and was far more convenient for the preparation of the more hindered olefins. In particular, the *t*-butyl derivative **110** (Table 3) could not be prepared using the phosphonium salt method, but was obtained in very good yield from the phosphonate.

The phosphonium salt method (Method A) also appeared to give a higher isomeric ratio than the other method. Typically, Method A gave *E/Z* ratios[53] of 4.5–6 to 1, while Method B gave ratios closer to 2 to 1.

In those cases in which the carbonyl compound had an α-alkoxy substituent, we encountered a further complication. In addition to the desired 2-methoxyacrylonitriles, we also isolated significant amounts of the material in which the double bond had isomerized to give the enol ethers (Scheme 46). In particular, in the reaction of phenylmethoxy acetone (**111**),[54] along with methoxyacrylonitrile **112**, we isolated 11% of a mixture of enol ethers **113**.



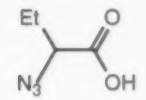
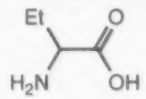
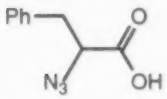
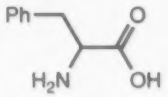
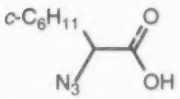
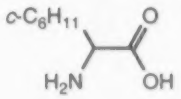
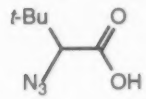
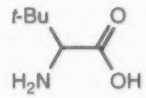
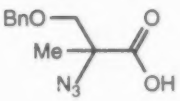
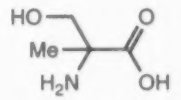
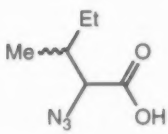
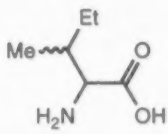
111 **112** **113**

Scheme 46

With the required methoxyacrylonitriles in hand, we attempted the azidonitration–hydrolysis sequence.

Table 4 shows the azido acids that were prepared by this methodology. The reaction was found to be useful for the

Table 4. Synthesis of Azido Acids and Amino Acids

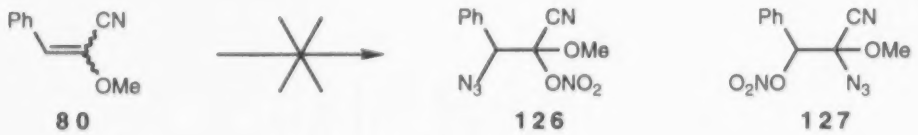
Azido Acid		Yield[a]	Amino Acid		Yield
	**104**	50%		**105**	76%
	**116**	65%		**131**	75%
	**119**	59%		**132**	86% 69%[b]
	**122**	40%		**133**	76%
	**125**	57%[c]		**134**	79%
	**146**	54%[d]		**142**	83%[e]

a) For 3 step sequence. b) Using PPh_3, H_2O, THF for the reduction. c) contains ca 6% impurity, which was removed in the next step. d) Isomer ratio 1.8 : 1 (^1H NMR). e) Ratio alloisoleucine : isoleucine 1.7 : 1 (^1H NMR).

preparation of azido acids substituted by primary (**104**, **116**), secondary (**119**) and tertiary (**122**) alkyl groups, and also for the α-alkylated azido acid **125**. The yields for the three-step sequence were in the range of 40–65%, which corresponds to an average of 74–87% for each step.

Although not all of the intermediates (azido nitrates and azido acetates) for the above transformations were characterized, they all had infrared spectra consistent with the proposed structures.

When we attempted the azidonitration of the aryl substituted methoxyacrylonitrile **80**, we encountered some difficulty. Although the reaction after workup appeared to be clean by TLC, concentration of the solution, even at low (<20°C) temperatures, lead to rapid decomposition of the product, with the visible evolution of a gas, possibly hydrogen cyanide or hydroazoic acid. When we attempted to obtain the NMR spectra of the material the sample continued to decompose, such that considerable pressure built up in the NMR tube.



80 **126** **127**

Scheme 47

It was not clear at this point if the problem encountered was due to the high instability of compound **126**, or if indeed this compound was never formed. Although the infrared spectrum of the crude reaction product did indicate the presence of both the azide and the nitrate functional groups, it was also possible that the adduct was the isomeric azido nitrate **127**. This would not be unexpected, as azide radical addition in this direction would give a benzylic radical.

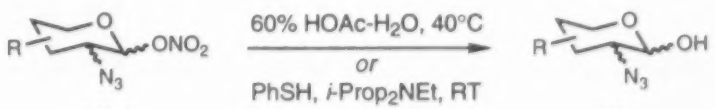
In any case, even when the three step azidonitration–

hydrolysis sequence was performed without ever concentrating the intermediates, no azido acid was ever isolated.

We also tried to develop another, more direct, sequence for the transformation of the initial azidonitration products to the azido acids.

Our initial efforts were aimed at the direct hydrolysis of the azido nitrates to the azido acids. We tried a variety of methods commonly used for the hydrolysis of acetals,[55] including acidic hydrolysis with hydrochloric acid or trifluoroacetic acid, and treatment with trimethylsilyl iodide, but we were never able to isolate any azido acid products. These methods all gave either no reaction or a complex mixture of products.

We next tried some methods that had been described for the conversion of azido nitrates derived from anhydro sugars to the corresponding azido sugars (Scheme 48). For example, one report described the conversion of **128** to **129** by warming in aqueous acetic acid.[45a] Under the same conditions, our azido nitrates gave little, if any of the hydrolyzed material.



128 **129**

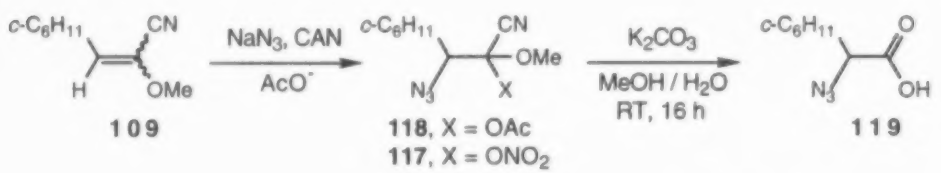
Scheme 48

Another report described the same transformation by treatment of the crude azido nitrate in acetonitrile with thiophenol and Hünig's base.[45b,c] Once again, our azido nitrates gave no hydrolysis

product under the same conditions.

We also tried adding Meerwein's salt to the crude azido nitrate, in the hope that one of the nitrate oxygens would be methylated, thus making it easier to displace. However, no reaction was apparent, and addition of water gave no azido acid.

In another attempt to shorten the sequence, we tried to introduce the acetate directly in the first step, by adding large amounts of acetate ion to the reaction mixture (Scheme 49). We felt that if the mechanism of the azidonitration involves addition of nitrate ion as the last step (as described later), that we might be able to replace it with a group which would be more easily hydrolyzed.



Scheme 49

We first tried adding a large excess (10 equivalents) of sodium acetate to the reaction mixture under the usual conditions used for the azidonitrations. After workup, we isolated what appeared (^{1}H NMR, IR) to be a mixture of azido acetate **118** and azido nitrate **117**, with the latter being the major component. After hydrolysis of the crude mixture under the usual conditions, we isolated azido acid **119** in 36% overall yield. Although this was an encouraging result, it was not an improvement over the original sequence.

We felt that if we could increase the solubility of the acetate anion relative to the nitrate anion, we could improve the ratio of azido acetate formed. Addition of tetraethylammonium acetate or tetrabutylammonium acetate to the reaction mixture led to the formation of the azido nitrate **117**, with only a trace of the azido acetate detected (^{1}H NMR). Finally, we thought that in order to form the azido acetate preferentially it would be neccessary to perform the reaction in the absence of nitrate anion. We tried the reaction of the methoxyacrylonitrile **80** using as oxidizing agent ceric ammonium sulfate in place of ceric ammonium nitrate, and adding a large excess of sodium acetate. When the reaction was performed at -10°C, most of the starting material remained after stirring overnight, and little, if any, azido acetate was formed. When the reaction was performed at room temperature, much starting material still remained, but extensive decomposition was evident. Apparently ceric ammonium sulfate is less reactive than the nitrate, possibly due to lower solubility in the reaction medium, or to a resulting lower oxidation potential.

We also tried using other oxidizing agents and/or solvents for the generation of the azido radical. The critical factor in the success of the azidonitration is maintaining a low enough concentration of azido radical so that nitrogen evolution is suppressed, yet still generating enough of it to add to the olefins at an appreciable rate.[44]

When the reaction with ceric ammonium nitrate is performed in dry acetonitrile, nitrogen evolution is at such a slow rate that addition to the olefin apparently can compete, especially at reduced

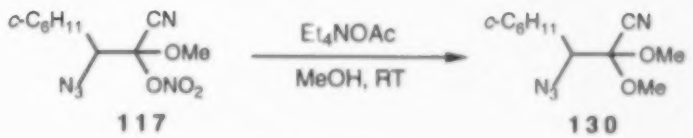
temperatures. In dry acetone, however, nitrogen is evolved very quickly, while in dry dioxane or THF no nitrogen evolution is observed. The addition of small amounts of water to these solvents increases the rate of nitrogen evolution dramatically. It appears from our limited survey of solvents that acetonitrile is ideally suited to the reaction of CAN and sodium azide, which are just soluble enough to react slowly.

We also tried a variety of oxidizing agents to determine their reactivity towards azide ion. Some of these (potassium persulfate, potassium permanganate) gave no reaction, even in water, while potassium peroxymonosulfate (*OXONE*) and periodic acid were too reactive in aqueous acetonitrile, but not reactive at all in the absence of water. None of the above combinations of oxidizing agent and solvent was more suited to the reaction than that described originally.

Finally, we were satisfied that our original sequence for the conversion of the azido nitrate into the azido acid may be the most efficient, but we wanted to develop a milder method of converting the azido nitrate into the azido acetate.

Instead of heating the azido nitrate with sodium acetate in acetic acid, we tried treatment with tetraethylammonium acetate in methanol. After being stirred at room temperature for two days all of the starting material had been consumed, but the product was not the azido acetate (^{1}H NMR). The IR spectrum of the material suggested the presence of an azide, but no nitrate or carbonyl group was indicated. It seemed that the nitrate had actually been dis-

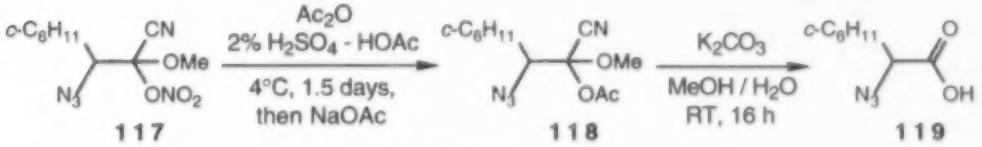
placed by methanol to give the acetal **130**.



117 **130**

Scheme 50

We then tried a method described in the literature for a carbohydrate-derived analogue.[45d] The azido nitrate **117** (Scheme 51) was dissolved in a 1:1 mixture of acetic anhydride and 2% sulfuric acid in acetic acid. After 36 hours, sodium acetate was added to the reaction mixture, and the product was extracted with dichloromethane. The azido acetate **118** was isolated as an impure oil, which was hydrolyzed to give the azido acid in 38% overall yield from the methoxyacrylonitrile **109**.



117 **118** **119**

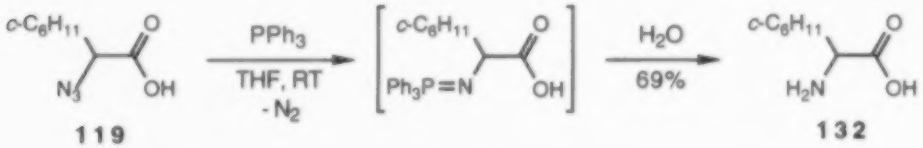
Scheme 51

Despite these efforts, we were not able to develop a route to the azido acids that was superior to the original, refined method.

The azido acids could all be transformed into the corresponding amino acids (Table 4) by hydrogenation (at atmospheric pressure or at 50 psi) over palladium.[52b] The amino acids were characterized spectroscopically, and by comparison with authentic samples where these were available.

In the case of azido acid **125**, hydrogenolysis of the benzyl group occurred concommitantly with azide reduction, to give α-methyl serine (**134**).

There are also other, more selective, methods for the reduction of azido acids.[52] For example, we transformed one of the azido acids (**119**) to the amino acid **132** by treatment with triphenylphosphine and water[56,52e,f] (Scheme 52). Although this method gave a somewhat lower yield of the amino acid than direct hydrogenation, it could prove useful in cases where there are other functional groups which could also be affected by the hydrogenation conditions. For example, it would allow the preparation of amino acids containing isolated double bonds.



119 **132**

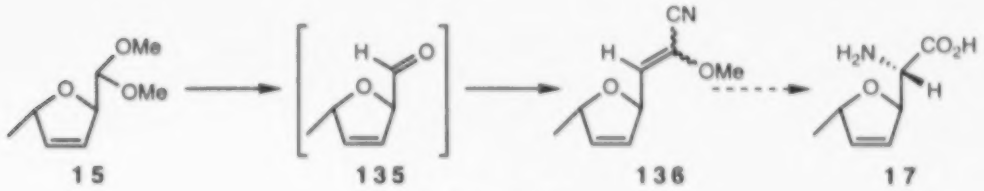
Scheme 52

Stereoselectivity of the Reaction

We were also interested in determining if our reaction sequence would show any stereoselectivity if the starting material had a stereogenic center in the side chain.

We chose furanomycin (**17**, Scheme 53) as our target for this purpose. This example would not only answer the question of the stereoselectivity of the reaction, but would also serve to demonstrate if the azidonitration could be performed in the presence of an isolated double bond.

Joullié's synthesis of furanomycin[9,10a] (see Scheme 8) involved the conversion of acetal **15** into an equal mixture of protected amino acids, reportedly via hydrolysis to the unstable aldehyde **135**. This aldehyde seemed to be a useful starting material for our sequence.



15 **135** **136** **17**

Scheme 53

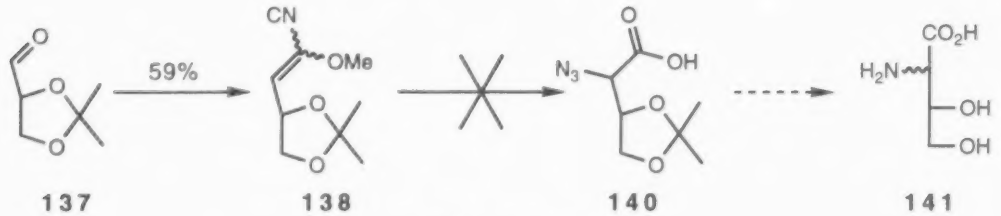
We prepared acetal **15** by the sequence reported by Joullié.[9] However, attempted hydrolysis of **15** according to the reported procedure, and in-situ olefination, gave less than 10% of methoxyacrylonitrile **136** (Scheme 53). Both methods used for the olefination failed to give adequate quantities of **136** for our purpose.

It was not evident from our observations if indeed aldehyde **135** was ever formed under the hydrolysis conditions. More likely, the hydrolysis gave only the hemi-acetal which, although adequate for Joullié's synthesis, might be problematic to us.

It also appeared probable that the adjacent stereogenic center would be epimerized under our reaction conditions, in view of our isolation of the isomerized side-products in the olefination of **111**. We therefore decided to use a simpler and more stable aldehyde than **135**.

We chose the protected glyceraldehyde derivative **137**[57]

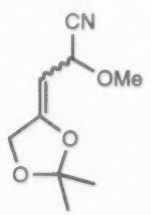
(Scheme 54) for its easy accessibility and relative stability.



137 **138** **140** **141**

Scheme 54

The required methoxyacrylonitrile **138** was formed in good yield, although we had some difficulty in the separation of the two isomers of **138** from the enol ethers **139** which were also formed. As a result, most of the material was not obtained in greater than 85% isomeric purity. However, we estimate (^{1}H NMR) that the total yield of methoxyacrylonitrile **138** is 61%, with the *E/Z* isomer ratio close to 7.5 to 1, and that the total yield of the enol ethers **139** is 31%. Also, although the starting aldehyde was prepared optically pure, it was not determined whether any optical activity was retained through this transformation.

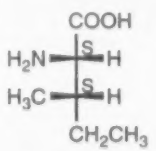


139

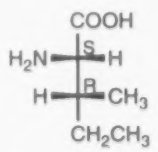
At any rate, when we subjected **138** to our reaction sequence, we were not able to isolate the expected azido acid **140**. The acetal protective group was clearly not stable to the reaction conditions,

and any product resulting from the deprotection of the diol would be highly water soluble. Even when we subjected the entire aqueous phase from the hydrolysis to the hydrogenation conditions, we were not able to separate any amino acid product from the inorganic salts. Mass spectroscopy of the crude reaction mixture did not show any amino acid **141**.

Finally, we decided to test the stereoselectivity of the reaction on a much simpler aldehyde, which we knew would be able to survive the reaction conditions. We chose for this purpose 2-methylbutyraldehyde, because of its easy availability, and because the products of the reaction sequence would be isoleucine (**142a**) and alloisoleucine (**142b**), which were both available for comparison. This would allow us not only to determine if there is any stereoselectivity, but also the sense of that selectivity.

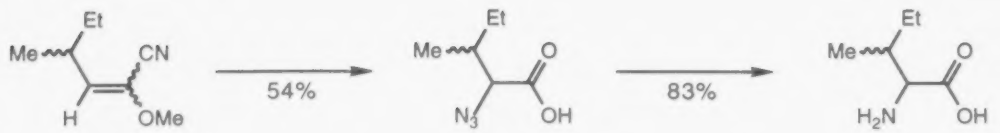


L-isoleucine
142a



L-alloisoleucine
142b

The methoxyacrylonitrile **143** (Scheme 55) was prepared by the phosphonate method. Azidonitration and hydrolysis gave the azido acid **146** as a mixture of isomers in a 1.8 to 1 ratio, as determined by ^{1}H NMR. Hydrogenation gave the amino acid **147**, which was shown by comparison with authentic samples to be composed of alloisoleucine and isoleucine in a 1.7 to 1 ratio.

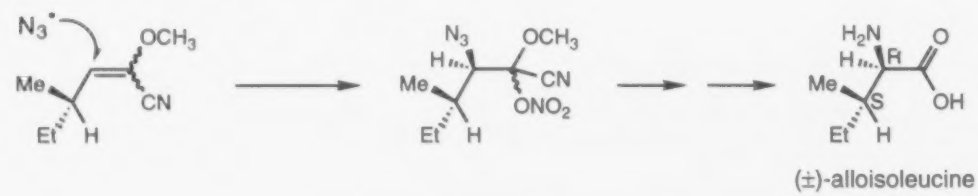


143 **146** **142**

Scheme 55

Although this isomer ratio of less than two to one represents a diastereoselectivity under 30%, it is significant in that it shows that the azidonitration does demonstrate some facial selectivity, even in such a minimally biased system.

Several models exist to explain the stereoselectivity of additions to double bonds. One simple model[58] is that in which the smallest group (in this case hydrogen) eclipses the double bond, and the radical then attacks from the least crowded face (Scheme 56). In our reaction sequence, following this model would lead to the preferential formation of the (2*R*,3*S*)-isomer (and its enantiomer), and indeed alloisoleucine is the major product.

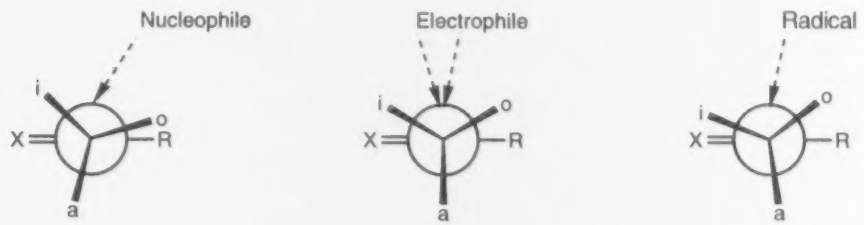


(±)-alloisoleucine

Scheme 56

However, ab initio calculations[59] of the preferred trajectories and conformational preferences for addition reactions have shown that the double bond is not eclipsed in the transition state (Scheme 57). Conversely, the allylic bonds are staggered with respect to the C=X axis (see Scheme 57). Calculations have also shown different

attack trajectories for nucleophiles, electrophiles, and radicals. Nucleophiles attack at angles greater than 120° (eg 123° for H^-) with respect to the C=X axis, while electrophiles attack at much more acute angles (eg 59° for H^+ or 101° for BH_3). Radicals attack at an angle in between the two (eg 102° for $H^\bullet$).

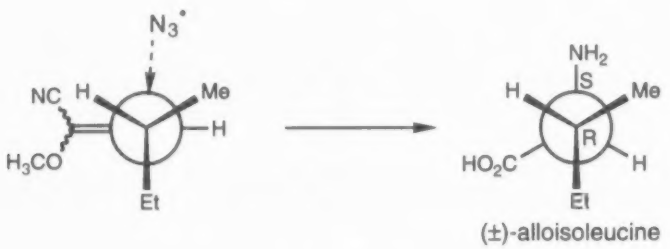


Scheme 57

Based on a model in which one of the positions labelled a, i, or o is a methyl group, and the other two are hydrogens, calculations were performed in order to determine the relative energies of transition states with the methyl in the anti (a), outside (o), and inside (i) positions (Scheme 57). For both the nucleophilic and electrophilic cases, the lowest energy transition state had methyl in the anti position. When the attacking species was removed from the calculated transition states, the conformation with the methyl in the inside position had the highest energy. However, for nucleophilic attack, the transition state substituted in the outside position is of higher energy than that substituted in the inside position, by a factor of two to one. The preferred transition state for any nucleophilic attack should therefore have the smallest substituent in the outside position. On the other hand, for the attack of an electro-

phile at an acute angle, the transition state substituted in the inside position is of tenfold higher energy than that substituted in the outside position. These models lead to the expectation of opposite stereoselectivity for the addition of nucleophiles and electrophiles. Although these last calculations were not specifically performed for the attack of a radical species, the transition state substituted on the inside would be expected to be of higher energy, although the energy difference would likely be less dramatic than in the electrophilic case.

Application of the staggered model to the analysis of our system would place the smallest substituent in the inside position (see Scheme 58). Following through the sequence once again predicts the preferential formation of (±)-alloisoleucine. However, it is appreciated that we do not know the stereoselectivity of the reaction for each individual isomer, and so this analysis may be incomplete.



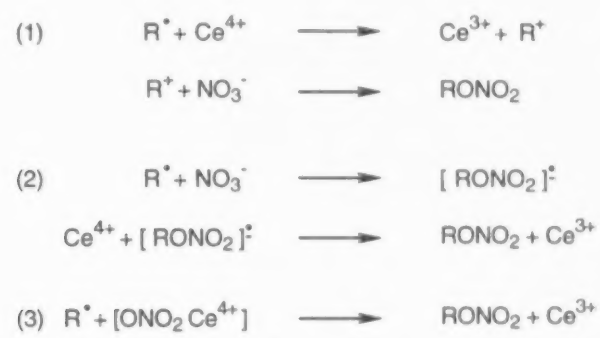
Scheme 58

Mechanistic Considerations

It has been proposed[42,44] that azidonitrations involve initial addition to the olefins of either the free azido radical, or of a ceric-

azide complex. The relatively low oxidation potential of the azide anion (0.78 eV vs SCE)[60,61] suggests that it may easily be oxidized by the ceric ion to give the azido radical.

The radical species resulting from such additions could be converted to the nitrate by one of several pathways (Scheme 59).[62]



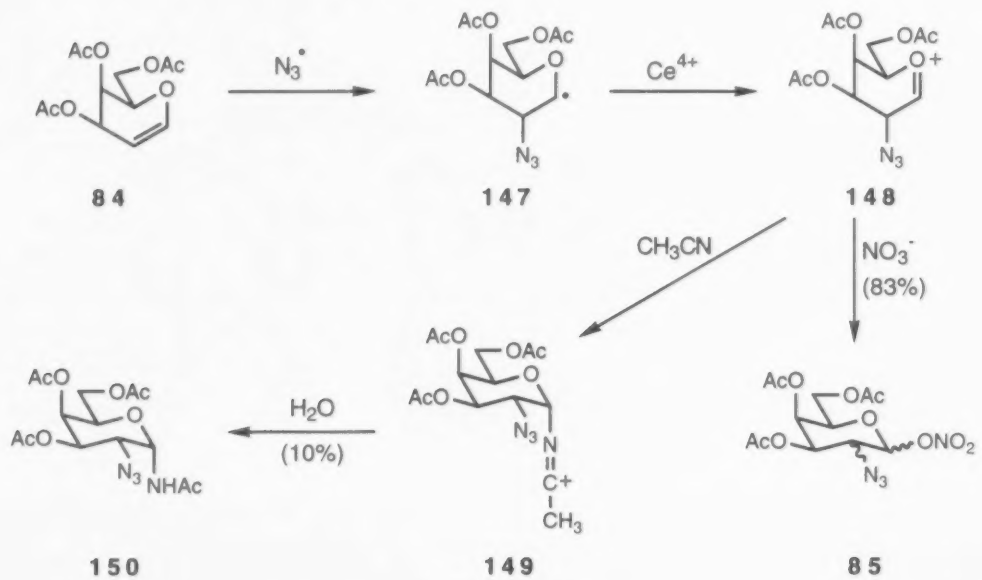
Scheme 59

In the first pathway, the initially formed radical is oxidized by electron transfer from ceric ion to form the carbocation, which then accepts nitrate. Alternatively (pathway 2) the radical first forms a complex with nitrate, which is then oxidized by ceric ion. In the final suggested pathway, the nitrate is formed by ligand transfer from a cerium-nitrate complex.

It has been suggested[62] that the latter pathways may be more important for primary radicals, while secondary and tertiary radicals may be more susceptible to electron transfer from the ceric ion.

In Lemieux's[44] azidonitration of anhyro sugars, along with azido nitrates **85**, a small amount (10%) of amide **150** (Scheme 60) was isolated. The formation of **150** is consistent with the proposed

intermediacy of cation **148**, which can be trapped by nitrate ion to give **85**, or by the solvent acetonitrile to give, after hydrolysis, amide **150**.

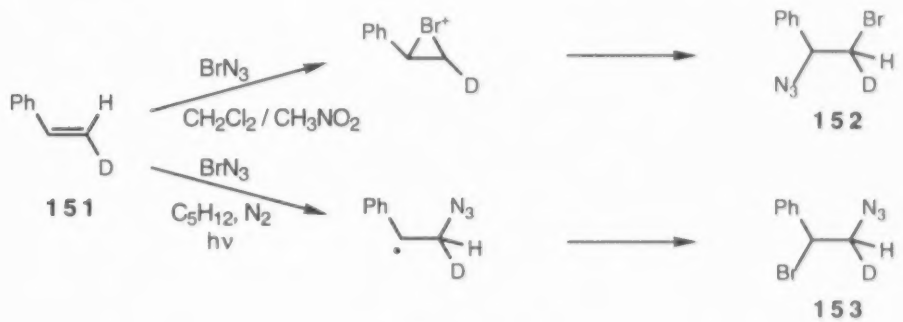


Scheme 60

The question of whether the initial addition is indeed a radical process remained unanswered. There is evidence in the literature for the existence of the azido radical, including spectroscopic evidence for its formation during flash photolysis experiments.[63]

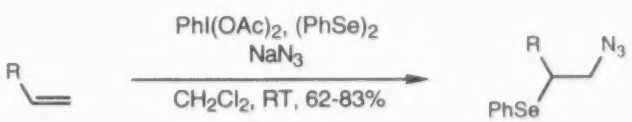
A report of the azidobromination of styrene has suggested that different mechanisms may be involved in the reaction, depending on the conditions.[64] Addition of bromine azide under ionic conditions (use of polar solvents) to styrene **151** proceeds exclusively with Markovnikov regioselectivity to give the internal azide **152** (Scheme 61). On the other hand, treatment under radical

conditions (irradiation in an inert, degassed solvent) gives the terminal azide **153** as the only product. This regioselectivity can be explained by the initial addition of the azido radical to the terminus of the double bond, thereby generating a benzylic radical.



Scheme 61

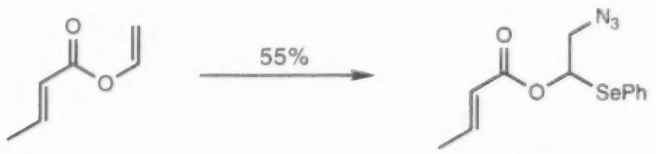
A recent report detailed the azido-phenylselenation of double bonds under conditions that seem to promote a radical process.[61] Unlike the usual addition of nucleophiles initiated by electrophilic phenylselenium species,[65] treatment of terminal olefins with (diacetoxyiodo)benzene, diphenyl diselenide, and sodium azide gives almost exclusively the anti-Markovnikov products (Scheme 62). It was also shown that the reaction does not proceed with exclusive trans stereoselectivity, as is usual for electrophilic processes.



Scheme 62

This azido-phenylselenation has also been shown to favor

electron-rich olefins. Although, unlike Trahanovsky's azidonitrations, electron-poor double bonds are attacked, the vinyl crotonate **154** is selectively functionalized at the electron-rich site (Scheme 63).

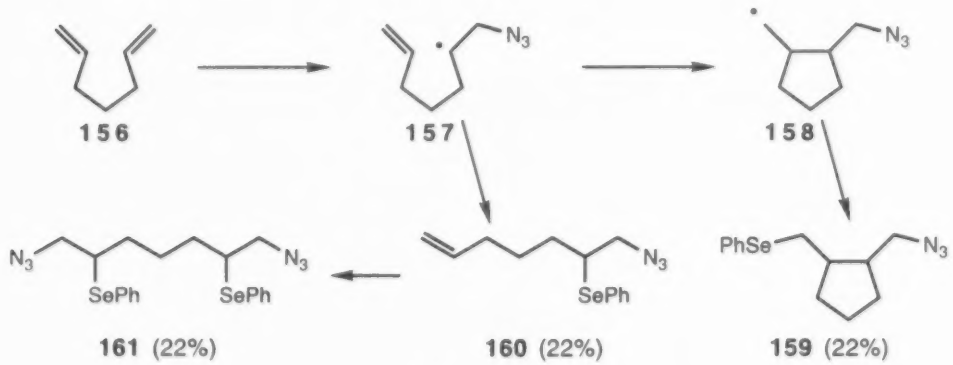


154 **155**

Scheme 63

The authors proposed that the reaction course involves the initial oxidation of azide by the hypervalent iodine reagent to give the azido radical, which adds to the olefin to afford a carbon radical; the latter is then trapped by diphenyl diselenide. Several experiments were performed in order to support this interpretation.

First, the reaction of 1,6-heptadiene (**156**) was carried out, with the expectation that the initially formed radical **157** would rapidly cyclize to give, after trapping by diphenyl diselenide, cyclo



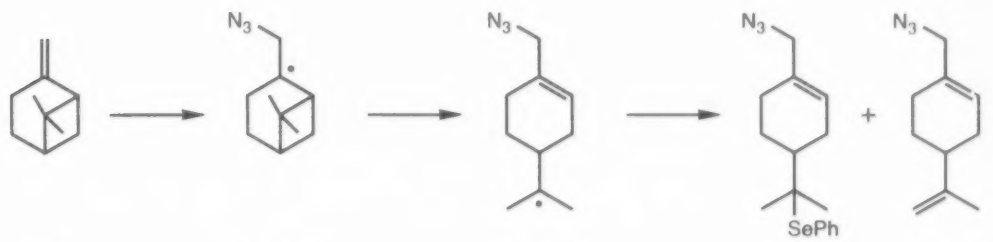
156 **157** **158**

161 (22%) **160** (22%) **159** (22%)

Scheme 64

pentane **159** (Scheme 64). In fact, **159** was isolated, along with equal amounts of the products of azido-phenylselenation of one (**160**) or both (**161**) double bonds.

Further evidence for a radical mechanism was provided by the reaction of β-pinene (**162**). In this case, the initially formed radical **163** (Scheme 65) would be expected to fragment to give the more stable radical **164**, and in fact the isolation of the two products **165** and **166** indicate that this has indeed occurred.



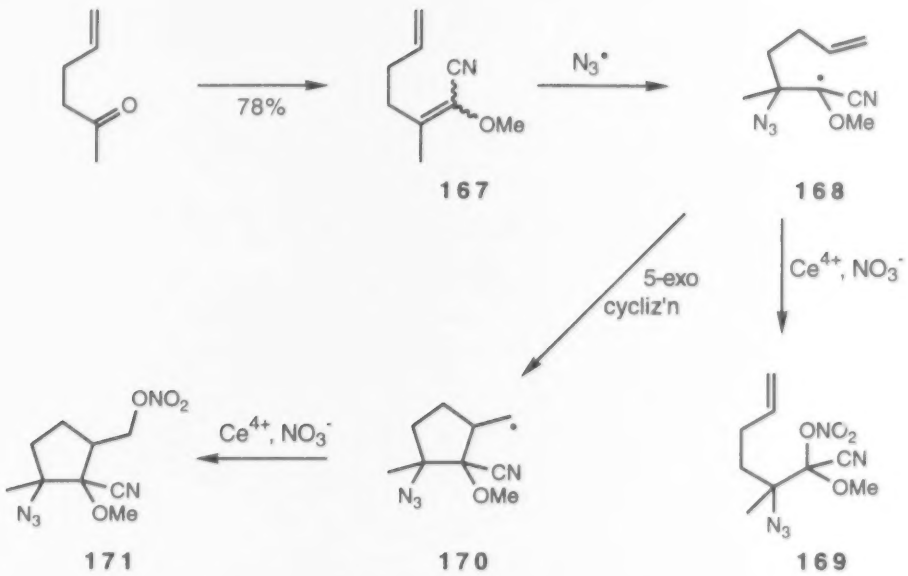
162 **163** **164** **165** (35%) **166** (31%)

Scheme 65

We set out to determine if a radical intermediate in our reaction could similarly be trapped other than by formation of the normal azido nitrate product. Our intention was to construct a system such that the initially formed radical could add to a suitably placed double bond within the molecule. We chose methoxyacrylonitrile **167**, readily available from 5-hexen-2-one (Scheme 66).

If the radical **168** is the initial product of azide radical addition, then two modes of reaction would be plausible. First, oxidation and addition of nitrate would give the normal azido nitrate **169**. Alternatively, 5-*exo* radical cyclization would give the pri-

mary radical **170**, which could then be oxidized to give cyclic azido nitrate **171**.



Scheme 66

When we subjected **167** to the usual azidonitration conditions, we isolated a material which appeared by its NMR spectra to be the normal azido nitrate 169. Although this material could not be fully characterized due to its instability (decomposition was evident even during the NMR aquisition time), the ^{1}H and ^{13}C NMR clearly showed the presence of a terminal double bond.

From these observations, we cannot conclusively determine that no cyclized material **171** was formed, but it does not appear to be a major product. The question that remains is whether the radical **168** is indeed not formed as an intermediate in the azidonitration, or whether it simply is not reactive enough to cyclize prior to

oxidation by ceric ion. We have been able to find no examples in the literature of the cyclization of such capto-dative radicals.[32]

As an aside, the apparent formation of **169** as the major product in the azidonitration of **167** has shown that it is possible to add preferentially to the functionalized double bond. Evidently the methoxyacrylonitrile moiety is significantly more reactive than is the isolated double bond.

Although we have not been able to conclusively demonstrate that the reaction follows a radical mechanism, it is clear that the reaction involves initial attack of either the azido radical or of a ceric-azide complex, to form a stabilized, capto-dative radical.

Conclusion

We have developed a new synthetic route which provides access to a variety of amino acids in five steps from carbonyl compounds. The reaction sequence has proved to be amenable to various aldehydes and ketones, with the exception of aryl aldehydes, and those with substituents which are highly sensitive to acidic conditions.

Significantly, the sequence is suited to the formation of α-substituted amino acids from ketones. Such amino acids are said to possess interesting biological activities.

The reaction has also shown some degree of stereoselectivity, even in a system which would be expected to show little steric bias. Further work is required in order to determine if this selectivity can be improved by adjustment of the reaction conditions, and if

other systems show a higher degree of selectivity. In particular, it will be interesting to note if cyclic systems, or those containing substituents that may complex the reagent, may lead to high diastereoselectivity. It may also be found that other types of substrates (eg silyl enol ethers similar to **92**, Scheme 41) are equally suited to this methodology.

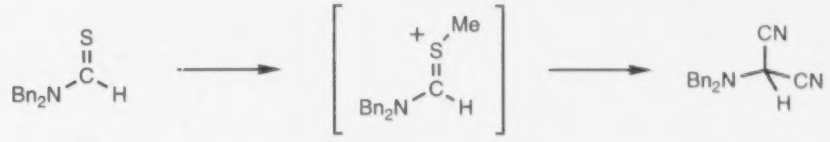
III EXPERIMENTAL

General Procedures

The same general procedures were used as described on page 61. The following particulars also apply. Purification of amino acids was accomplished by ion exchange chromatography using Dowex 50W-X8 (20–50 mesh) strongly acidic resin. Typically, one gram of the resin was packed in a disposable Pasteur pipette (5 3/4 in) such that the flow rate of water through the column was 15–20 drops per minute, the flow rate being largely controlled by how tightly the cotton plug was packed. The resin was washed sequentially with 1 N NaOH (3 column volumes), H_2O until neutral (pH Hydrion paper, range 1–12), 1.2 N HCl (3 column volumes), and then H_2O until the washings were neutral. The amino acid was dissolved in 1.2 N HCl, and the solution was evaporated to dryness as indicated below. The residual protonated amino acid (50–150 mg) was then applied as an aqueous solution (3–5 mL). The column was washed with water to remove any impurities, and then the amino acids were eluted with 1 N NH_3. Aqueous solutions of amino acids were evaporated in vacuo (0.5–2 mm) at 40–50°C using a rotary evaporator fitted with a dry-ice condenser. Silica TLC plates for amino acids were developed using 4:1:1 *n*-butyl alcohol–acetic acid–H_2O, then sprayed with a 0.2% solution of ninhydrin in ethanol and heated on a hotplate. Proton NMR spectra of amino acids were recorded in D_20 or DCl (1 N), and are reported relative to external

TSP. ^{13}C NMR spectra of amino acids are reported relative to dioxane as an internal standard.

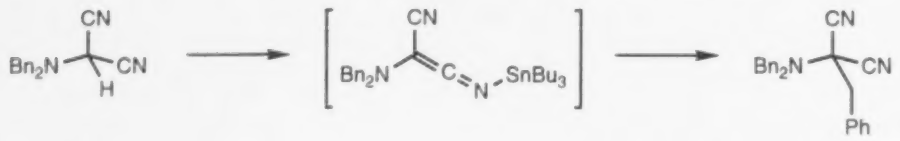
[Bis(phenylmethyl)amino]malononitrile (41).



45 **41**

This compound was made previously in this laboratory[21] using a slightly different procedure. A general literature procedure[66] was followed. A solution of **45** (0.6408 g, 2.66 mmol) and methyl iodide (1.0 mL, 16 mmol) in dry CH_2Cl_2 (25 mL) was refluxed overnight, and then evaporated. The residue was dissolved in dry acetonitrile (15 mL) and mercuric cyanide (0.671 g, 2.66 mmol) was added. After the mixture had, been stirred for 5 h the reaction was incomplete (TLC, 10:1 hexanes–ethyl acetate). A further portion of mercuric cyanide (0.35 g, 1.4 mmol) was added, and the mixture was stirred overnight. The mixture was filtered through Celite, and the filtrate evaporated. Flash chromatography of the residue over silica gel, using 10:1 hexanes–ethyl acetate, gave **41** (569.4 mg, 82%) as a white solid: FT-IR (CH_2Cl_2 cast) 3031, 2902, 2848, 1495, 1455 cm^{-1}; ^1H NMR $CDCl_3$, 300 MHz) δ 3.79 (s, 4 H), 4.64 (s, 1 H), 7.30–7.44 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 44.24, 55.89, 110.27, 128.60, 129.01, 129.04, 135.23; exact mass, *m/z* calcd for $C_{17}H_{15}N_3$ 261.1266, found 261.1267.

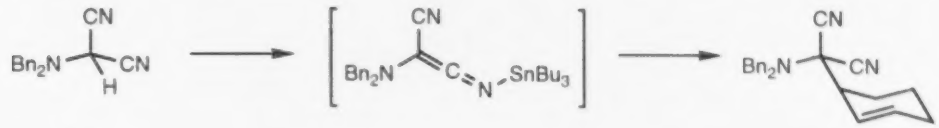
[Bis(phenylmethyl)amino](phenylmethyl)malononitrile (43).



41 **43**

This experiment has been done before in this laboratory,[21] but the procedure has been modified. Tributyl(diethylamino)-stannane (365.0 mg, 1.008 mmol) was added to **41** (258.2 mg, 0.988 mmol) in dry benzene (4 mL), and the solution was refluxed overnight. The intermediate had characteristic[24b] bands at 2090 and 2190 cm^{-1} in its IR spectrum. Benzyl bromide (0.50 mL, 4.2 mmol) in benzene (2 mL) was added in one portion. The solution was refluxed a further 4 h, and then evaporated. Flash chromatography of the residue over silica gel, using first hexanes and then 19:1 hexanes–ethyl acetate, gave an impure white solid which was recrystallized from CH_2Cl_2–hexanes to give **43** (227.5 mg, 65%) as a homogeneous (^1H NMR, 200 MHz) white crystalline solid: mp 154–155°C [mp[21] 162–4°C (hexanes–ethyl acetate)]; FT-IR (CH_2Cl_2 cast) 1602, 1586, 1495, 1455, 748, 743, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.14 (s, 2 H), 4.05 (s, 4 H), 7.20–7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 44.42, 56.15, 64.00, 113.29, 127.90, 128.57, 128.64, 128.81, 130.69, 131.35, 137.03; exact mass, *m/z* calcd for $C_{24}H_{21}N_3$ 351.1735, found 351.1742. Anal. Calcd for $C_{24}H_{21}N_3$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.93; H, 5.77; N, 12.05.

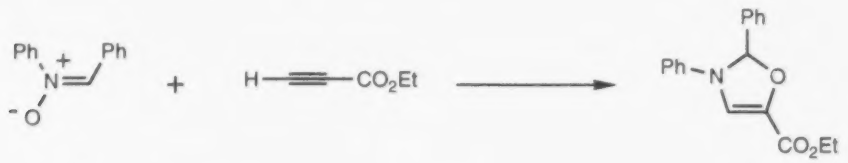
[Bis(phenylmethyl)amino](2-cyclohexenyl)malononitrile (47).



41 **47**

Tributyl(diethylamino)stannane (360.7 mg, 0.996 mmol) was added to **41** (251.2 mg, 0.961 mmol) in dry benzene (4 mL), and the solution was refluxed overnight. 3-Bromo-1-cyclohexene (0.40 mL, 3.5 mmol) in benzene (2 mL) was added in one portion. The solution was refluxed a further 4 h, and then evaporated. Flash chromatography (two times) of the residue over silica gel using first hexanes and then 19:1 hexanes–ethyl acetate gave **47** (140 mg, 40%) as a homogeneous (^{1}H NMR, 200 MHz) white solid: mp 67.5–68°C; FT-IR ($CHCl_3$ cast) 1600, 1580, 1495, 1454, 1382, 750, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22–2.14 (m, 6 H), 2.91–3.08 (m, 1 H), 3.93 (s, 4 H), 5.75–5.86 (m, 1 H), 5.96–6.08 (m, 1 H), 7.14–7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.06, 24.84, 25.24, 41.58, 55.57, 66.14, 112.60, 113.05, 122.27, 127.79, 128.42, 128.99, 133.66, 136.28; exact mass, *m/z* calcd for $C_{23}H_{23}N_3$ 341.1897, found 341.1890. Anal. Calcd for $C_{23}H_{23}N_3$: C, 80.90; H, 6.79; N, 12.31. Found: C, 81.02; H, 6.57; N, 12.39.

3-Ethoxycarbonyl-1,5-diphenyl-4-oxazoline (55).



54 **55**

A general literature procedure[31] was followed. A solution of nitrone **54**[67] (1.06 g, 5.37 mmol) and ethyl propiolate (0.56 mL, 5.53 mmol) in dry benzene (30 mL) was refluxed overnight under argon. The solvent was evaporated, and the residue recrystallized from ether to give **55** (0.27 g, 17%) as a white, homogeneous (TLC, silica, 4:1 hexanes–ethyl acetate) solid: mp 164–165°C); FT-IR (CH_2Cl_2 cast) 1690, 1640, 1600, 1510, 1365, 1335, 1265, 1230, 1010, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.32 (t, J = 7 Hz, 3 H), 4.38 (dq, J = 3, 7 Hz, 2 H), 6.64–6.76 (m, 2 H), 6.83–6.97 (m, 2 H), 7.14–7.59 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.40, 60.56, 97.10, 114.60, 121.33, 127.01, 128.32, 128.99, 129.51, 129.99, 131.96, 136.97, 139.85, 160.39; exact mass, m/z calcd for $C_{18}H_{17}NO_3$ 295.1208, found 295.1204.

2-Methoxy-2-pentenenitrile (68).

68

A general literature procedure was followed.[38] Propionaldehyde (0.36 mL, 5.0 mmol) and then triethylamine (1.55 mL,

11.0 mmol) were added to a stirred solution of (cyanomethoxymethyl)triphenylphosphonium bromide[38] (4.12 g, 10.0 mmol) in anhydrous CH_2Cl_2 (100 mL). After being stirred overnight, the solution was washed with dilute HCl (1.2 N, 2 x 100 mL) and H_2O (100 mL), dried ($MgSO_4$) and concentrated to a small volume. The remaining solution was diluted with ether, filtered, and evaporated. Kugelrohr distillation of the residue (85–90°C, 23 mm Hg) gave **68** (427.9 mg, 77%, 95% pure) as a colorless liquid composed of two isomers in a 5.8:1 ratio, and also containing a small amount (*ca* 5% w/w) of methoxyacetonitrile: FT-IR (CH_2Cl_2 cast) 2970, 2939, 2120, 1727, 1463, 1123, 971 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 0.99, 1.06 (two t, J = 7.5 Hz, 3 H), 2.20, 2.26 (two p, J = 7.5 Hz, 2 H), 3.60, 3.70 (two s, 3 H), 5.53, 5.55 (two t, J = 7.5 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 13.16, 14.32, 19.10, 21.87, 57.11, 58.94, 113.97, 114.67, 121.73, 129.84, 130.00, 131.71; exact mass, *m/z* calcd for C_6H_9NO 111.0684, found 111.0687.

3-Phenyl-2-methoxyacrylonitrile (80).[41]

80

A general literature procedure was followed.[38] Benzaldehyde (2.20 mL, 21.6 mmol) and then triethylamine (3.10 mL, 22.2 mmol) were added to a stirred solution of (cyanomethoxymethyl)triphenylphosphonium bromide[38] (8.24 g, 21.6 mmol) in anhydrous CH_2Cl_2 (200 mL). After being stirred overnight, the solution was

diluted with *n*-pentane (200 mL), and filtered. The filtrate was washed with HCl (1.2 N, 2 x 200 mL), H_2O (2 x 200 mL) and brine (200 mL), dried ($MgSO_4$) and evaporated. Kugelrohr distillation of the residue (105°C, 0.5 mm Hg) gave **80** (1.5468 g, 49%) as a colorless oil composed of two isomers in a 4.1:1 ratio: FT-IR (CH_2Cl_2 cast) 2230, 2213, 1623, 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.71, 3.86 (two s, 3 H), 6.13, 6.48 (s, 1 H), 7.23–7.39 (m, 3 H), 7.47–7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 357.24, 58.73, 114.43, 120.34, 122.53, 127.96, 128.48, 128.71, 128.92, 129.76, 130.10, 131.42; exact mass, *m/z* calcd for $C_{10}H_9NO$ 159.0684, found 159.0685.

2-Azido-1-nitratodiethyl ether (99).

69 **99**

Dry acetonitrile (5 mL) and then ethyl vinyl ether (0.30 mL, 3.1 mmol) were added to a cooled (-5°C) mixture of ceric ammonium nitrate (1.6518 g, 3.01 mmol) and sodium azide (99.5 mg, 1.53 mmol). The mixture was then stirred vigorously at -5°C overnight, and then diluted with ice-cold ether (5 mL) and ice-cold H_2O (5 mL). The layers were separated, and the organic phase was washed with ice-cold H_2O (2 x 5 mL) and brine (2 x 5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using CH_2Cl_2, gave **99** (23.0 mg, 9%) as a homogeneous (TLC, 4:1 hexanes–ethyl acetate) colorless oil: ^1H NMR

($CDCl_3$, 200 MHz) δ 1.31 (t, J = 7 Hz, 3 H), 3.27 (dd, J = 4.5, 13 Hz, 1 H), 3.45 (dd, J = 6, 13 Hz, 1 H), 3.67 (dq, J = 9.5, 7 Hz, 1 H), 3.92 (dq, J = 9.5, 7 Hz, 1 H), 4.55 (dd, J = 4.5, 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.95, 53.56, 65.87, 90.32.

2-Azidobutanoic acid (104).[68]

68 **102** **103** **104**

A solution of **68** (164.5 mg, 1.48 mmol) in dry acetonitrile (8 mL) was added to a cooled (-10°C) mixture of ceric ammonium nitrate (2.62 g, 4.78 mmol) and sodium azide (147.5 mg, 2.27 mmol). The mixture was then stirred vigorously at -10 to -5°C overnight, and then diluted with ice-cold ether (7 mL) and ice-cold H_2O (7 mL). The layers were separated, and the organic phase was washed with ice-cold H_2O (2 x 7 mL), dried ($MgSO_4$), and evaporated to give crude **102**.

The crude azido nitrate was dissolved in glacial HOAc (6 mL). Sodium acetate (0.73 g) was added, and the solution was heated to 100°C for 1 h. The solution was cooled, diluted with CH_2Cl_2 (15 mL), and then washed with H_2O (15 mL), saturated aqueous $NaHCO_3$ (2 x 15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated to give crude **103**.

The crude azido acetate was dissolved in 75% aqueous methanol (8 mL). Anhydrous K_2CO_3 (0.76 g) was added, and the mixture was stirred overnight at room temperature. The mixture

was diluted with H_2O (30 mL) and washed with CH_2Cl_2 (3 x 15 mL). The aqueous phase was acidified with HCl (4 N), and then extracted with CH_2Cl_2 (4 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **104** (95.2 mg, 50% from **68**) as a light yellow, homogeneous (^1H NMR, 200 MHz) oil: FT-IR (CH_2Cl_2 cast) 3097 (br), 2110, 1720 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.06 (t, J = 7.5 Hz, 3 H), 1.71–2.07 (m, 2 H), 3.90 (dd, J = 5, 8 Hz, 1 H), 9.64 (br s, 1 H); ^{13}C NMR (D_2O, 75.5 MHz) δ 10.42, 25.79, 67.22, 178.77; exact mass, m/z calcd for $C_4H_7N_3O_2$ 129.0538, found 129.0535.

In a separate experiment, the crude material from the first step was purified by flash chromatography over silica gel, using 10:1 hexanes–ethyl acetate, to give **102** (40%) as a colorless oil composed of two isomers: FT-IR (CH_2Cl_2 cast) 2113, 1675, 1293 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.12 (dt, J = 2.5, 7.5 Hz, 3 H), 1.53–1.96 (m, 2 H) 3.74 (ddd, J = 3.5, 4.5, 11 Hz, 1 H), 3.83, 3.90 (two s, 3 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 35.49, 35.60, 58.10, 58.26, 66.81, 67.51, 111.35, 127.92, 129.36, 129.77, 135.96.

In another experiment, the azido acetate **103** (76%) was isolated as an impure yellow oil: IR (CH_2Cl_2 cast) 2120, 1774 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (dt, 3.83 J = 2, 6 Hz, 3 H), 1.53–1.97 (m, 2 H), 2.20 (s, 3 H), 3.70, 3.72 (two s, 3 H), 3.74–3.90 (m, 1 H).

DL-2-Aminobutanoic acid (105).

104 **105**

104 (64.3 mg, 0.498 mmol) in ethanol (5 mL) was shaken with 10% Pd/C (30 mg) under hydrogen (50 psi) for 2 h. The mixture was filtered through Celite, acidified with HCl (1.2 N, 5 mL) and evaporated. Ion exchange chromatography of the residue as described above gave crude **105** (47.1 mg, 91%). Compound **105** (30.0 mg) was recrystallized from H_2O–ethanol to give the pure material (25.1 mg, 76%) as a white, homogeneous (^1H NMR, 200 MHz), crystalline solid: mp 213–217°C (sublimes) [mp of authentic sample (Eastman) 212–215°C (sublimes)]; FT-IR (KBr) 3400 (br), 1593 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 0.97 (t, J = 7.5 Hz, 3 H), 1.89 (p, J = 7 Hz, 2 H), 3.70 (t, J = 6 Hz, 1 H); ^{13}C NMR (D_2O, 125.7 MHz) δ 9.35, 24.53, 56.71, 175.70.

4-Phenyl-2-methoxycrotonitrile (108).

108

A general literature procedure was followed.[38] Phenylacetaldehyde (0.99 g, 8.24 mmol) and then triethylamine (1.40 mL, 10.0 mmol) were added to a stirred solution of (cyanomethoxymethyl)triphenylphosphonium bromide[38] (4.03 g, 9.78 mmol) in anhydrous CH_2Cl_2 (100 mL). After being stirred overnight, the

solution was evaporated to 30 mL, diluted with *n*-pentane (200 mL) and filtered. The filtrate was washed with HCl (1.2 N, 2 x 100 mL), H_2O (2 x 100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated. Kugelrohr distillation of the residue (95°C, 0.01 mm Hg) gave **108** (1.12 g, 78%) as a pale yellow oil composed of two isomers in a 4.5:1 ratio (^1H NMR, 200 MHz): FT-IR (CH_2Cl_2 cast) 2233, 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.53, 3.59 (two d, J = 8 Hz, 3 H), 3.63, 3.79 (two s, 3 H), 5.65, 5.69 (two t, J = 8 Hz, 1 H), 7.18–7.33 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 31.60, 34.43, 57.28, 59.06, 114.07, 118.37, 126.09, 126.91, 127.10, 128.66, 128.72, 129.03, 129.09, 132.67, 139.15; exact mass, *m/z* calcd for $C_{11}H_{11}NO$ 173.0840, found 173.0842.

3-Cyclohexyl-2-methoxyacrylonitrile (109).

109

A general literature procedure was followed.[41] Diethyl cyano(methoxy)methylphosphonate[41] (1.8664 g, 9.01 mmol) in dry THF (10 mL) was added to a suspension of NaH (60% w/w in oil, 404 mg, 10.1 mmol) in THF (30 mL). After H_2 evolution ceased, the mixture was refluxed for 15 min. Cyclohexanecarboxaldehyde (679.8 mg, 6.06 mmol) in THF (10 mL) was added, and the solution was refluxed a further 3 h. After being cooled, the solution was diluted with H_2O (300 mL) and brine (10 mL), and extracted with ether (3 x 125 mL). The combined organic extracts were washed

with H_2O (2 x 150 mL) and brine (150 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 *n*-pentane–ether, gave **109** (0.85 g, 85%) as a colorless oil composed of two isomers in a 1.8:1 ratio (^1H NMR, 200 MHz): FT-IR (CH_2Cl_2 cast) 2929, 2853, 2232, 1635, 1450, 1205 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.03–1.47 (m, 5 H), 1.57–1.81 (m, 5 H), 2.23–2.66 (m, 1 H), 3.58, 3.69 (two s, 3 H), 5.38, 5.42 (d, J = 10 Hz, d, J = 9.5 Hz, 1 H total); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 25.88, 25.94, 26.03, 26.17, 32.37, 33.67, 35.16, 38.03, 57.09, 59.04, 114.16, 114.81, 125.76, 128.91, 130.76, 133.77; exact mass, *m/z* calcd for $C_{10}H_{15}NO$ 165.1154, found 165.1149.

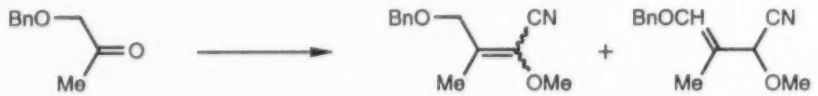
2-Methoxy-4,4-dimethyl-2-pentenenitrile (110).

110

A general literature procedure was followed.[41] Diethyl cyano(methoxy)methylphosphonate[41] (3.6387 g, 17.6 mmol) in dry THF (10 mL) was added to a suspension of NaH (60% w/w in oil, 752.0 mg, 18.8 mmol) in THF (30 mL). After H_2 evolution ceased, the mixture was refluxed for 20 min. Trimethylacetaldehyde (1.0164 g, 11.8 mmol) in THF (10 mL) was added, and the solution was refluxed a further 3 h. After being cooled, the solution was diluted with H_2O (500 mL), and extracted with ether (3 x 200 mL). The combined organic extracts were washed with H_2O (2 x 250 mL) and brine (250 mL), dried ($MgSO_4$) and evaporated. Flash chro-

matography of the residue over silica gel, using *n*-pentane, gave **110** (1.3312 g, 81%) as a colorless oil composed of two isomers in a 1.8:1 ratio (^{1}H NMR, 200 MHz): FT-IR (CH_2Cl_2 cast) 2965, 2233, 2217, 1628, 1465, 1235, 1157 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 200 MHz) δ 1.13, 1.21 (two s, 9 H), 3.56, 3.69 (two s, 3 H), 5.43, 5.62 (two s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 29.68, 30.46, 31.25, 33.57, 57.31, 58.80, 114.80, 114.91, 129.47, 129.56, 132.14, 137.23; exact mass, *m/z* calcd for $C_8H_{13}NO$ 139.0997, found 139.1000.

2-Methoxy-3-methyl-4-phenylmethoxycrotonitrile (112).



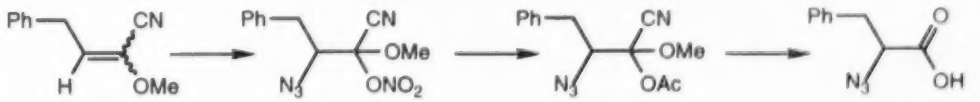
111 **112** **113**

A general literature procedure was followed.[41] Diethyl cyano(methoxy)methylphosphonate[41] (1.2473 g, 6.02 mmol) in dry THF (3 mL) was added to a suspension of NaH (60% w/w in oil, 287.1 mg, 7.18 mmol) in THF (9 mL). After H_2 evolution ceased, the mixture was refluxed for 15 min. Phenylmethoxyacetone (**111**)[54] (668.2 mg, 4.07 mmol) in THF (3 mL) was added, and the solution was refluxed a further 3 h. After being cooled, the solution was diluted with H_2O (200 mL) and brine (10 mL), and extracted with ether (3 x 65 mL). The combined organic extracts were washed with H_2O (2 x 75 mL) and brine (75 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 4:1 hexanes–ether, gave **112** (598.9 mg, 67%) as a colorless oil composed of two isomers in a 1.7:1 ratio (^{1}H NMR, 200 MHz): FT-

IR (CH_2Cl_2 cast) 2215, 1652, 1073 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.85, 1.97 (two s, 3 H), 3.66, 3.71 (two s, 3 H), 4.17, 4.18 (two s, 2 H), 4.44, 4.48 (two s, 2 H), 7.31–7.36 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 13.53, 15.99, 58.92, 59.32, 66.39, 70.82, 72.70, 72.86, 113.06, 113.46, 128.08, 128.17, 128.73, 133.78, 134.46, 138.46, 138.55, 148.07; exact mass, *m/z* calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1101.

Compound **113** (98.5 mg, 11%) was also isolated as a colorless, homogeneous (TLC, 4:1 hexanes –ether) oil: FT-IR (CH_2Cl_2 cast) 1730, 1682, 1455, 1171, 1154, 1101, 1080 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.71, 1.72 (two s, 3 H), 3.32 (s, 3 H), 4.40 (s, 1 H), 4.67 (s, 2 H), 6.45 (m, 1 H), 7.26–7.43 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 9.89, 56.41, 72.59, 74.79, 108.30, 117.17, 127.84, 128.55, 128.95, 137.34, 147.39; exact mass, *m/z* calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1098.

2-Azido-3-phenylpropanoic acid (116).[6,56,68-70]



108 **114** **115** **116**

A solution of **108** (169.8 mg, 0.98 mmol) in dry acetonitrile (5 mL) was added to a cooled (-15°C) mixture of ceric ammonium nitrate (1.7590 g, 3.21 mmol) and sodium azide (102.1 mg, 1.57 mmol). The mixture was then stirred vigorously at -15°C overnight, and then diluted with ice-cold ether (5 mL) and ice-cold H_2O (5 mL). The layers were separated, and the organic phase was washed

with ice-cold H_2O (2 x 5 mL), dried ($MgSO_4$), and evaporated to give crude **114**.

The crude azido nitrate was dissolved in glacial HOAc (2.5 mL). Sodium acetate (0.31 g) was added, and the solution was heated to 100°C for 1 h. The solution was cooled, diluted with CH_2Cl_2 (20 mL), and then washed with H_2O (4 x 15 mL), dried ($MgSO_4$) and evaporated to give crude **115**.

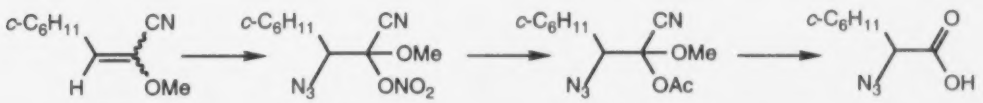
The crude azido acetate was dissolved in 75% aqueous methanol (4 mL). Anhydrous K_2CO_3 (0.85 g) was added, and the mixture was stirred overnight at room temperature. The mixture was diluted with H_2O (10 mL) and washed with CH_2Cl_2 (2 x 15 mL). The aqueous phase was acidified with concentrated HCl, and then extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **116** (121.7 mg, 65% from **108**) as a yellow, homogeneous (^1H NMR, 200 MHz) oil: FT-IR (CH_2Cl_2 cast) 3090 (br), 2117, 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.03 (dd, J = 9, 14 Hz, 1 H), 3.24 (dd, J = 5, 14 Hz, 1 H), 4.14 (dd, J = 5, 9 Hz, 1 H), 7.22–7.40 (m, 5 H), 10.00 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 37.51, 63.10, 127.45, 128.80, 129.23, 135.62, 175.66; exact mass, m/z calcd for $C_9H_9N_3O_2$ 191.0695, found 191.0689.

In a separate experiment, azido nitrate **114** (93%) was isolated as an impure oil: IR (CH_2Cl_2 cast) 2120, 1665, cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 2.76–2.93 (m, 1 H), 3.14 (dd, J = 3, 14 Hz, 1 H), 3.84, 3.88 (two s, 3 H) 4.04–4.14 (m, 1 H), 7.25–7.40 (m, 5 H); ^{13}C

NMR (CD_2Cl_2, 50.3 MHz) δ 35.49, 35.60, 58.10, 58.26, 66.81, 67.51, 111.35, 127.92, 129.36, 129.77, 135.96.

In another experiment, azido acetate **115** (78%) was isolated as an impure yellow oil: IR (CH_2Cl_2 cast) 2110, 1750 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 2.08, 2.15 (two s, 3 H), 2.78–2.93 (m, 1 H), 3.02–3.19 (m, 1 H), 3.71, 3.74 (two s, 3 H), 4.12–4.24 (m, 1 H), 7.22–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 20.66, 34.75, 35.13, 56.19, 66.15, 66.58, 91.02, 98.08, 112.46, 127.25, 128.80, 129.24, 136.09, 168.21.

2-Azido-2-cyclohexylacetic acid (119).[11]



109 **117** **118** **119**

A solution of **109** (166.9 mg, 1.01 mmol) in dry acetonitrile (5 mL) was added to a cooled (-15°C) mixture of ceric ammonium nitrate (1.70 g, 3.10 mmol) and sodium azide (99.3 mg, 1.53 mmol). The mixture was then stirred vigorously at -15°C overnight, and then diluted with ice-cold ether (5 mL) and ice-cold H_2O (5 mL). The layers were separated, and the organic phase was washed with ice-cold H_2O (2 x 5 mL), dried ($MgSO_4$), and evaporated to give crude **117**.

The crude azido nitrate was dissolved in glacial HOAc (4 mL). Sodium acetate (0.33 g) was added, and the solution was heated to 100°C for 1 h. The solution was cooled, diluted with CH_2Cl_2 (15 mL),

and then washed with H_2O (15 mL) and dilute aqueous $NaHCO_3$ (2 x 15 mL), dried ($MgSO_4$) and evaporated to give crude **118**.

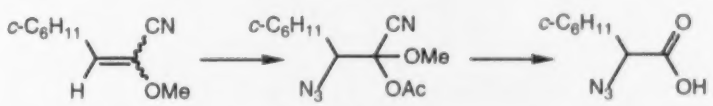
The crude azido acetate was dissolved in 75% aqueous methanol (4 mL). Anhydrous K_2CO_3 (0.61 g) was added, and the mixture was stirred overnight at room temperature. The mixture was diluted with H_2O (20 mL) and washed with CH_2Cl_2 (3 x 10 mL). The aqueous phase was acidified with HCl (4 N), and then extracted with CH_2Cl_2 (4 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **119** (108.6 mg, 59% from **109**) as an off-white, homogeneous (^1H NMR, 200 MHz) solid: mp 69–72°C; FT-IR (CH_2Cl_2 cast) 3050 (br), 2107, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.03-1.42 (m, 5 H), 1.52-2.10 (m, 6 H), 3.75 (d, J = 6 Hz, 1 H), 10.78 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 25.76, 25.88, 28.28, 29.78, 40.20, 67.43, 176.19; exact mass, *m/z* calcd for $C_8H_{12}NO_2$ $(M - H, -N_2)^+$ 154.0868, found 154.0873; CIMS, *m/z* 210 $(M + NH_4)^+$.

In a separate experiment, the crude material from the first step was purified by flash chromatography over silica gel, using CH_2Cl_2, to give **117** (76%) as an unstable colorless oil: IR (CH_2Cl_2 cast) 2115, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10-1.46 (m, 5 H), 1.58-2.05 (m, 6 H), 3.64-3.79 (m, 1 H), 3.82, 3.86 (two s, 3 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 25.74, 26.07, 27.66, 28.02, 31.01, 31.12, 38.46, 38.78, 54.82, 57.33, 69.93, 71.14, 103.05, 103.88, 110.94, 111.09.

In another experiment, the crude azido acetate was partially purified by flash chromatography over silica gel using CH_2Cl_2 to

give **118** (71%) as an impure oil: IR (CH_2Cl_2 cast) 2110, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10-2.00 (m, alkyl H), 2.18 (two s, 3 H), 3.70 (two s, 3 H), 3.84-3.92 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 20.90, 21.10, 24.06-31.18 (alkyl CH_2's), 38.18, 38.54, 55.41, 55.96, 70.00, 70.25, 97.97, 112.86, 168.10.

2-Azido-2-cyclohexylacetic acid (119).[11]

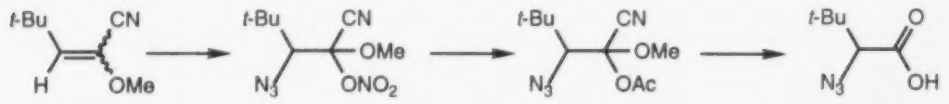


109 **118** **119**

A solution of **109** (165.2 mg, 1.000 mmol) in dry acetonitrile (5 mL) was added to a cooled (-15°C) mixture of ceric ammonium nitrate (1.77 g, 3.23 mmol), sodium azide (101.4 mg, 1.56 mmol) and sodium acetate (0.87 g, 10.6 mmol). The mixture was then stirred vigorously at -15°C overnight, and then diluted with ice-cold ether (10 mL) and ice-cold H_2O (10 mL). The layers were separated, and the organic phase was washed with ice-cold H_2O (2 x 5 mL), dried ($MgSO_4$), and evaporated to give an oil composed of azido acetate **118** and azido nitrate **117** (IR, TLC, silica, 10:1 hexanes–ethyl acetate). The crude mixture was dissolved in 75% aqueous methanol (4 mL). Anhydrous K_2CO_3 (0.51 g) was added, and the mixture was stirred overnight at room temperature. The mixture was diluted with H_2O (20 mL) and washed with CH_2Cl_2 (3 x 10 mL). The aqueous phase was acidified with HCl (4 N), and then extracted with CH_2Cl_2 (4 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **119** (66.3 mg, 36%) as

an off-white, homogeneous (^{1}H NMR, 200 MHz) solid, identical to that prepared previously.

2-Azido-3,3-dimethylbutanoic acid (122).[11,70,71]



110 **120** **121** **122**

A solution of **110** (159.2 mg, 1.14 mmol) in dry acetonitrile (5 mL) was added to a cooled (-20°C) mixture of ceric ammonium nitrate (2.02 g, 3.68 mmol) and sodium azide (109.4 mg, 1.68 mmol). The mixture was then stirred vigorously at -20°C overnight, and then diluted with ice-cold ether (5 mL) and ice-cold H_2O (5 mL). The layers were separated, and the organic phase was washed with ice-cold H_2O (2 x 5 mL), dried ($MgSO_4$), and evaporated to give crude **120**.

The crude azido nitrate was dissolved in glacial HOAc (4 mL). Sodium acetate (0.44 g) was added, and the solution was heated to 100°C for 1 h. The solution was cooled, diluted with CH_2Cl_2 (20 mL), and then washed with H_2O (15 mL) and saturated aqueous $NaHCO_3$ (2 x 15 mL), dried ($MgSO_4$) and evaporated to give crude **121**.

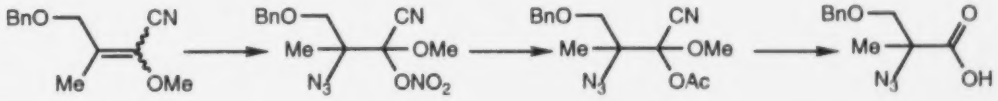
The crude azido acetate was dissolved in 75% aqueous methanol (4 mL). Anhydrous K_2CO_3 (0.54 g) was added, and the mixture was stirred overnight at room temperature. The mixture was diluted with H_2O (20 mL) and washed with CH_2Cl_2 (3 x 10 mL). The aqueous phase was acidified with HCl (4 N), and then extracted with CH_2Cl_2 (4 x 15 mL). The combined organic extracts were dried

($MgSO_4$) and evaporated to give **122** (71.4 mg, 40% from **110**) as a colorless, homogeneous (^1H NMR, 300 MHz) oil: FT-IR (CH_2Cl_2 cast) 3000 (br), 2108, 1715 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.07 (s, 9 H), 3.79 (s, 1 H), 10.10 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 26.66, 35.94, 72.07, 175.19; CIMS, *m/z* 175 $(M + NH_4)^+$.

In a separate experiment, azido nitrate **120** (79%) was isolated as an impure, unstable oil: IR (CH_2Cl_2 cast) 2115, 1660 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.10, 1.12 (two s, 9 H), 3.75 (s, 1 H), 3.81, 3.84 (two s, 3 H).

In another experiment, azido acetate **121** (57%) was isolated as an unstable, very impure oil: IR (CH_2Cl_2 cast) 2110, 1750 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.08, 1.12 (two s, 9 H), 2.17, 2.18 (two s, 3 H), 3.66, 3.68 (two s, 3 H), 3.76 (s, 1 H).

2-Azido-2-methyl-3-phenylmethoxypropanoic acid (125).



112 **123** **124** **125**

A solution of **112** (123.5 mg, 0.518 mmol) in dry acetonitrile (5 mL) was added to a cooled (-15°C) mixture of ceric ammonium nitrate (969.2 mg, 1.768 mmol) and sodium azide (53.8 mg, 0.828 mmol). The mixture was then stirred vigorously at -15°C overnight, and then diluted with ice-cold ether (5 mL) and ice-cold H_2O (5 mL). The layers were separated, and the organic phase was washed with ice-cold H_2O (2 x 5 mL), dried ($MgSO_4$), and evaporated to give crude **123**: IR (CH_2Cl_2 cast) 2135, 1675 cm^{-1}.

The crude azido nitrate was dissolved in glacial HOAc (4 mL). Sodium acetate (0.49 g) was added, and the solution was heated to 100°C for 1 h. The solution was cooled, diluted with CH_2Cl_2 (15 mL), and then washed with H_2O (15 mL) and saturated aqueous $NaHCO_3$ (2 x 15 mL), dried (Na_2SO_4) and evaporated to give crude **124**: IR (CH_2Cl_2 cast) 2135, 1740 cm^{-1}.

The crude azido acetate was dissolved in 75% aqueous methanol (4 mL). Anhydrous K_2CO_3 (0.59 g) was added, and the mixture was stirred overnight at room temperature. The mixture was diluted with H_2O (20 mL) and washed with CH_2Cl_2 (4 x 10 mL). The aqueous phase was acidified with HCl (4 N), and then extracted with CH_2Cl_2 (4 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **125** (75.9 mg, 57% from **112**) as a light yellow oil containing an impurity (*ca* 6 mole %, ^1H NMR): FT-IR (CH_2Cl_2 cast) 3200 (br), 2140, 2104, 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 3 H), 3.62 (d, J = 19 Hz, 1 H), 3.82 (d, J = 19 Hz, 1 H), 4.61 (s, 2 H), 7.27–7.40 (m, 5 H), 10.50 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.05, 66.31, 73.73, 74.74, 127.67, 127.95, 128.51, 137.21, 176.99; exact mass, *m/z* calcd for $C_{11}H_{12}NO_3$ (M -H, $-N_2)^+$ 206.0817, found 206.0820; CIMS, *m/z* 253 $(M + NH_4)^+$.

DL-Phenylalanine (131).[69]

116 **131**

Azide **116** (124.8 mg, 0.653 mmol) in ethanol (5 mL) was stirred with 10% Pd/C (60 mg) under hydrogen (atmospheric pressure) overnight. The mixture was filtered through Celite using HCl (1.2 N) to elute the product, and evaporated. Ion exchange chromatography of the residue as described above gave crude **131** which was recrystallized from 2:1 ethanol–H_2O to afford the pure material (80.5 mg, 75%) as a white, homogeneous (^{1}H NMR, 200 MHz), crystalline solid: mp 240°C (begins to sublime at 225°C) [mp of authentic sample 253°C (begins to sublime at 240°C)]; ^{1}H NMR (1.07 M DCl, 200 MHz) δ 2.97 (dd, J = 8, 16 Hz, 1 H), 3.01 (dd, J = 6, 16 Hz, 1 H), 4.13 (dd, J = 6, 8 Hz, 1 H), 7.02–7.23 (m, 5 H); ^{13}C NMR (1.07 M DCl, 75.5 MHz) δ 36.10, 54.64, 128.65, 129.84, 130.06, 134.45, 171.62.

DL-Cyclohexylglycine (132).[11,72]

119 **132**

Method A: Azide **119** (98.6 mg, 0.538 mmol) in ethanol (5 mL) was stirred with 10% Pd/C (45 mg) under hydrogen (atmospheric pressure) overnight. The mixture was diluted with HCl (1.2 N), filtered through Celite, and evaporated. Ion exchange chromatography of the residue as described above gave crude **132**, which was recrystallized from ethanol to give the pure material (72.9 mg, 86%) as a white, homogeneous (^{1}H NMR, 200 MHz), crystalline solid: mp 253–259°C (sublimes) [lit.[72] mp 260°C

(sublimes)]; ^{1}H NMR of HCl salt (D_2O, 300 MHz) δ 0.83–1.21 (m, 5 H), 1.40–1.66 (m, 5 H), 1.75–1.92 (m, 1 H), 3.76 (d, J = 4.5 Hz, 1 H); ^{13}C NMR of HCl salt (D_2O, 75.5 MHz) δ 25.97, 26.22, 28.34, 29.04, 39.29, 58.66, 172.23.

Method B: Triphenylphosphine (71.8 mg, 0.274 mmol) and then H_2O (9 μL, 0.5 mmol) were added to a solution of **119** (47.1 mg, 0.257 mmol) in dry THF (1.5 mL). The mixture was stirred overnight, diluted with benzene, and evaporated. The residue was partitioned between benzene (15 mL) and HCl (1.2 N, 20 mL). The layers were separated and the organic phase was extracted with HCl (1.2 N, 2 x 10 mL). The combined acidic extracts were washed with benzene (10 mL), and evaporated to give an oily solid. Ion exchange chromatography of the residue as described above gave **132** (27.8 mg, 69%) as a white solid, identical (^{1}H NMR, 200 MHz) to that prepared previously.

DL-*t*-Leucine (133).[11]

122 **133**

Azide **122** (38.4 mg, 0.244 mmol) in ethanol (4 mL) was stirred with 10% Pd/C (16 mg) under hydrogen (atmospheric pressure) overnight. The mixture was diluted with HCl (1.2 N), filtered through Celite, and evaporated. Ion exchange chromatography of the residue as described above gave crude **133** which was recrystallized by dissolving in a minimum of hot H_2O and precipi-

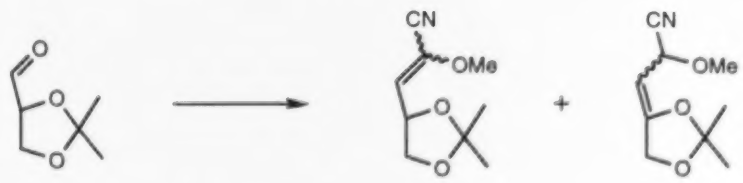
tating with acetone to afford the pure material (24.2 mg, 76%) as a white, homogeneous (^{1}H NMR, 200 MHz), crystalline solid: mp 215°C (sublimes) [mp of authentic sample (L-*t*-leucine, Sigma) 220°C (sublimes)]; ^{1}H NMR (D_2O, 200 MHz) δ 1.07 (s, 9 H), 3.43 (s, 1 H); ^{13}C NMR (D_2O, 75.5 MHz) δ 26.70, 32.77, 64.96, 174.69.

DL-α-Methylserine (134).

125 **134**

Azide **125** (74.0 mg, 0.315 mmol) in ethanol (5 mL) was stirred with 10% Pd/C (28 mg) under hydrogen (57 psi) for 18 h. The mixture was diluted with HCl (1.2 N), filtered through Celite, and evaporated. Ion exchange chromatography of the residue as described above gave crude **134** which was recrystallized from dilute ethanol to afford the pure material (29.7 mg, 79%) as a white, homogeneous (^{1}H NMR, 300 MHz), crystalline solid: mp 208°C (sublimes) [mp of authentic sample 210°C (sublimes)]; ^{1}H NMR (D_2O, 300 MHz) δ 1.44 (s, 3 H), 3.68 (d, J = 12 Hz, 1 H), 3.93 (d, J = 12 Hz, 1 H); ^{13}C NMR (D_2O, 75.5 MHz) δ 19.29, 63.34, 65.58, 176.15.

3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methoxyacrylonitrile (138).



137 **138** **139**

A general literature procedure was followed.[41] Diethyl cyano(methoxy)methylphosphonate[41] (3.96 g, 19.1 mmol) in dry THF (10 mL) was added to a suspension of NaH (60% w/w in oil, 0.82 g, 20.5 mmol) in THF (30 mL). After H_2 evolution ceased, the mixture was refluxed for 15 min. D-(+)-Glyceraldehyde dimethyl acetal (**137**)[57] (1.66 g, 12.76 mmol) in THF (10 mL) was added, and the solution was refluxed a further 3 h. After being cooled, the solution was diluted with H_2O (500 mL) and extracted with ether (3 x 200 mL). The combined organic extracts were washed with H_2O (2 x 250 mL) and brine (250 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 9:1 *n*-pentane–ether, gave two isomers of **138** and also two other isomers **139**, in which the double bond had isomerized. The less polar isomer of **138** (160.3 mg, 7%) was obtained as a pure (^{1}H NMR, 300 MHz) colorless oil: FT-IR (CH_2Cl_2 cast) 2988, 2222, 1650, 1456, 1373, 1223, 1062 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 1.34 (d, J = 0.5 Hz, 3 H), 1.38 (d, J = 0.5 Hz, 3 H), 3.59 (dd, J = 7, 8 Hz, 1 H), 3.76 (s, 3 H), 4.12 (dd, J = 6, 8 Hz, 1 H), 4.96 (ddd, J = 6.5, 7, 8 Hz, 1 H), 5.57 (d, J = 8 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 25.81, 26.75, 59.29, 69.22, 70.27, 110.03, 113.45, 124.67, 131.68; exact

mass, *m/z* calcd for $C_9H_{13}NO_3$ 183.0895, found 183.0895. The more polar isomer of **138** (1.2273 g, 52%, 85% pure) was obtained as a colorless oil, contaminated with *ca* 15% w/w of one of the double bond isomers **139** (^{1}H NMR, 300 MHz): FT-IR (CH_2Cl_2 cast) 2988, 2238, 1640, 1229, 1213, 1062 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 1.37 (s, 3 H), 1.42 (s, 3 H), 3.63 (dd, *J* = 6.5, 8.5 Hz, 1 H), 3.66 (s, 3 H), 4.17 (dd, *J* = 6, 8.5 Hz, 1 H), 4.83 (ddd, *J* = 6, 6.5, 9 Hz, 1 H), 5.42 (d, *J* = 9 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 25.79, 26.81, 57.35, 69.75, 73.44, 110.33, 113.21, 116.04, 134.85; exact mass, *m/z* calcd for $C_9H_{13}NO_3$ 183.0895, found 183.0893.

The less polar isomer of **139** (132.1 mg, 6%, 90% pure) was obtained as a colorless oil contaminated with *ca* 10% w/w of the less polar isomer of **138** (^{1}H NMR, 200 MHz) : FT-IR (CH_2Cl_2 cast) 2993, 1700, 1378, 1290, 1220, 1110 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 200 MHz) δ 1.48 (s, 6 H), 3.42 (s, 3 H), 4.46 (dt, *J* = 9, 1.5 Hz, 1 H), 4.56 (d, *J* = 1.5 Hz, 2 H), 4.96 (d, *J* = 9 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 25.12, 25.16, 56.79, 65.18, 67.02, 87.81, 114.43, 118.17, 159.06; exact mass, *m/z* calcd for $C_9H_{13}NO_3$ 183.0895, found 183.0893.

The other double bond isomer **139** was not separated from the remaining material.

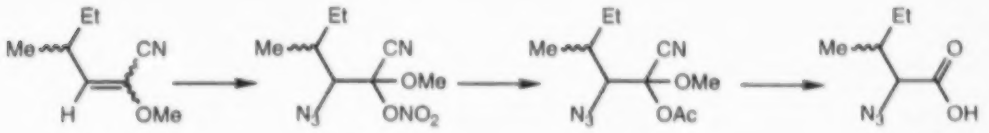
2-Methoxy-4-methyl-2-hexenenitrile (143).

143

A general literature procedure was followed.[41] Diethyl cyano(methoxy)methylphosphonate[41] (3.6206 g, 17.5 mmol) in dry THF (12 mL) was added to a suspension of NaH (60% w/w in oil, 780.7 mg, 19.5 mmol) in THF (30 mL). After H_2 evolution ceased, the mixture was refluxed for 30 min. 2-Methylbutyraldehyde (1.0255 g, 11.9 mmol) in THF (10 mL) was added, and the solution was refluxed a further 3 h. After being cooled, the solution was diluted with H_2O (500 mL) and brine (10 mL), and extracted with ether (3 x 200 mL). The combined organic extracts were washed with H_2O (2 x 250 mL) and brine (250 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 10:1 *n*-pentane–ether, and then Kugelrohr distillation (87–90°C, 20 mm Hg) gave **143** (1.4396 g, 87%) as a colorless oil composed of two isomers in a 1.7:1 ratio (^{1}H NMR, 300 MHz): FT-IR (CH_2Cl_2 cast) 2965, 2234, 2219, 1636, 1459, 1212, 1133 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 0.86, 0.88 (two t, J = 7.5 Hz, 3 H), 0.98, 1.06 (two t, J = 7 Hz, 3 H), 1.17–1.55 (m, 2 H), 2.34–2.72 (m, 1 H), 3.59, 3.69 (two s, 3 H), 5.29, 5.36 (d, J = 11 Hz, d, J = 10 Hz, 1 H total); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 11.87, 19.81, 21.12, 29.70, 30.56, 32.53, 35.75, 57.13, 58.94, 114.22, 114.72, 125.77, 129.54,

131.34, 134.25; exact mass, *m/z* calcd for $C_8H_{13}NO$ 139.0997, found 139.0987.

2-Azido-3-methylpentanoic acid (146).[56,68]



143 **144** **145** **146**

A solution of **143** (150.9 mg, 1.084 mmol) in dry acetonitrile (5 mL) was added to a cooled (-22°C) mixture of ceric ammonium nitrate (1.96 g, 3.58 mmol) and sodium azide (111.7 mg, 1.718 mmol). The mixture was then stirred vigorously at -22°C overnight, and then diluted with ice-cold ether (5 mL) and ice-cold H_2O (5 mL). The layers were separated, and the organic phase was washed with ice-cold H_2O (2 x 5 mL), dried ($MgSO_4$), and concentrated to 1 mL. Crude **144** had: IR (Et_2O cast) 2120, 1672 cm^{-1}.

Glacial HOAc (4 mL) was added to the crude azido nitrate, and the remaining ether was evaporated. Sodium acetate (0.44 g) was added, and the solution was heated to 100°C for 1 h. The solution was cooled, diluted with CH_2Cl_2 (15 mL), and then washed with H_2O (20 mL) and saturated aqueous $NaHCO_3$ (2 x 20 mL), dried ($MgSO_4$) and evaporated to give crude **145**: IR (CH_2Cl_2 cast) 2120, 1760 cm^{-1}.

The crude azido acetate was dissolved in 75% aqueous methanol (4 mL). Anhydrous K_2CO_3 (0.62 g) was added, and the mixture was stirred overnight at room temperature. The mixture

was diluted with H_2O (25 mL) and washed with CH_2Cl_2 (3 x 10 mL). The aqueous phase was acidified with HCl (4 N), and then extracted with CH_2Cl_2 (4 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **146** (91.8 mg, 54% from **143**) as a colorless oil composed of two isomers in a 1.8:1 ratio (^{1}H NMR, 300 MHz): FT-IR (CH_2Cl_2 cast) 3050 (br), 2112, 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91–1.06 (m, 6 H), 1.23–1.63 (m, 2 H), 1.95–2.10 (m, 1 H), 3.83, 4.00 (d, J = 6 Hz, d, J = 4.5 Hz, 1 H total), 10.10 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 11.25, 11.50, 14.64, 15.94, 24.94, 26.47, 37.22, 37.50, 66.08, 67.09, 176.36, 176.65; CIMS, *m/z* 175 $(M + NH_4)^+$.

Isoleucine and alloisoleucine (142).

146 **142**

Azide **146** (155.4 mg, 0.99 mmol) in 65% aqueous ethanol (6 mL) was stirred with 10% Pd/C (40 mg) under hydrogen (50 psi) for 2 h. The mixture was filtered through Celite, acidified with HCl (1.2 N), and evaporated. Ion exchange chromatography of the residue as described above gave **142** (107.8 mg, 83%) as a white crystalline solid composed of isoleucine and alloisoleucine in a 1:1.7 ratio (^{1}H NMR, 200 MHz): ^{1}H NMR (D_2O, 200 MHz) δ 0.89–1.03 (m, 6 H), 1.13–1.57 (m, 2 H), 1.87–2.16 (m, 1 H), 3.65, 3.72 (d, J = 4 Hz, d, J = 3.5 Hz, 1 H total); ^{13}C NMR (D_2O, 75.5 MHz) δ 11.84, 11.90,

14.12, 15.50, 25.26, 26.13, 36.43, 36.72, 59.32, 60.39, 175.05, 175.55.

2-Methoxy-3-methyl-2,6-heptadienenitrile (167).

167

A general literature procedure was followed.[41] Diethyl cyano(methoxy)methylphosphonate[41] (1.8776 g, 9.06 mmol) in dry THF (5 mL) was added to a suspension of NaH (60% w/w in oil, 404 mg, 10.1 mmol) in THF (18 mL). After H_2 evolution ceased, the mixture was refluxed for 15 min. 5-Hexene-2-one (610.2 mg, 6.22 mmol) in THF (5 mL) was added, and the solution was refluxed a further 3 h. After being cooled, the solution was diluted with H_2O (200 mL) and extracted with ether (3 x 60 mL). The combined organic extracts were washed with H_2O (3 x 100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 40:1 *n*-pentane–ether, gave **167** (737.8 mg, 78%) as a colorless oil composed of two isomers in a 1 to 1 ratio (^{1}H NMR, 200 MHz): FT-IR (CH_2Cl_2 cast) 2212, 1642, 1454, 1273, 1216, 1158 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 200 MHz) δ 1.78, 1.89 (two s, 3 H), 2.09–2.40 (m, 4 H), 3.63, 3.64 (two s, 3 H), 4.93–5.11 (m, 2 H), 5.67–5.91 (m, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 14.91, 18.26, 30.27, 31.52, 32.14, 33.80, 59.05, 59.15, 114.10, 114.20, 115.41, 115.86, 126.9, 127.06, 137.34, 137.79, 138.27, 138.34; exact mass, *m/z* calcd for $C_9H_{13}NO$ 151.0997, found 151.0999.

3-Azido-2-methoxy-3-methyl-2-nitrato-6-heptenenitrile (169).

167 **169**

A cooled (0°C) solution of **169** (141.2 mg, 0.934 mmol) in dry acetonitrile (5 mL) was added to a cooled (-13°C) mixture of ceric ammonium nitrate (1.2406 g, 2.26 mmol) and sodium azide (66.4 mg, 1.02 mmol). The mixture was then stirred vigorously at -18°C overnight, and then diluted with ice-cold ether (5 mL) and ice-cold H_2O (5 mL). The layers were separated, and the organic phase was washed with ice-cold H_2O (4 x 5 mL), dried ($MgSO_4$), and evaporated. Chromatography over Florisil, using 40:1 hexanes–ether, gave **169** (139.7 mg, 59%) as an impure, unstable yellow oil. This crude material had: IR (Et_2O cast) 2120, 1670 cm^{-1}; ^1H NMR (C_6D_6, 200 MHz) δ 0.99, 1.02 (two s, 3 H), 1.30–2.00 (m, 4 H), 3.32, 3.34 (two s, 3 H), 4.83–5.00 (m, 2 H), 5.41–5.64 (m, 1 H); ^{13}C NMR (C_6D_6, 50.3 MHz) δ 15.82, 17.39, 17.74, 27.89, 32.60, 34.08, 59.80, 69.16, 71.25, 115.57, 136.97. The ^{13}C NMR shows evidence of extensive decomposition during the acquisition time. However, both ^1H and ^{13}C NMR clearly demonstrate the presence of a terminal double bond.

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